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The development of a practical catalytic Petasus reaction of glycolaldehyde and the asymmetric allylboration of acyl cyanides

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Dissertation

THE DEVELOPMENT OF A PRACTICAL CATALYTIC PETASIS REACTION OF GLYCOLALDEHYDE AND THE ASYMMETRIC ALLYLBORATION OF ACYL CYANIDES

by

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DEDICATION

To my parents, Marie-Elena Jablonski and Joseph Summo, for their unconditional love and support. Without them, none of this would have been possible.

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THE DEVELOPMENT OF A PRACTICAL CATALYTIC PETASIS REACTION OF GLYCOLALDEHYDE AND THE ASYMMETRIC ALLYLBORATION OF ACYL CYANIDES

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Boston University Graduate School of Arts and Sciences, 2016

Major Professor: Scott E. Schaus, Associate Professor of Chemistry

ABSTRACT

Asymmetric nucleophilic boronate reactions have been developed using organic chiral diols, specifically binaphthols, as catalysts. A highly enantioselective allylboration of acyl cyanides under solvent-free conditions was catalyzed by (*S*)-Br_2BINOL. The reaction proceeds through single exchange of boronate with the chiral catalyst, promoted by *tert*-butanol. Allylation products were obtained in yields up to 97% and enantioselectivities up to 99:1 er. *Syn*- and *anti*-crotylborations of benzoyl cyanide were also performed, and the corresponding α-methyl products were isolated in good yields and moderate to good enantioselectivities, with the *E*-boronate producing a single diastereomer. This methodology represents a new route to enantioenriched homoallylic cyanohydrins through nucleophilic addition of the allyl group to acyl cyanides.

The enantioselective Petasis reaction of glycolaldehyde dimer to synthesize β-amino alcohols was also investigated. With commercially available aldehyde dimer, boronic acids, and amines, electron-rich α-arylglycinols were obtained in up to 92% yield and up to 99.5:0.5 er. Direct inject mass spectrometry studies revealed a single exchange between *p*-methoxyphenylboronic acid and (*S*)-Br_2BINOL, as well as coordination of the

imine intermediate to the catalyst-boronate complex. This reaction was further optimized to include electron-deficient boronic acids. Addition of Lewis acidic triethylborate had a two-fold effect on the reactivity; it facilitated both the exchange of boronic acid with catalyst, and the formation of the imine intermediate. Using chloroform as the solvent, and (*S*)-Ph_2BINOL, halogenated phenylboronic acids participated well in the Petasis reaction. This methodology is the first asymmetric Petasis reaction of glycolaldehyde to produce β-amino alcohols.

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LIST OF ABBREVIATIONS

Å.....angstrom

$[\alpha]_D$ ..... optical rotation at 589 nm

aq..... aqueous

Ar ..... aryl

BINOL ..... 1,1'-bi-2-naphthol

Bn.....benzyl

Boc .....*tert*-butoxycarbonyl

br ..... broad

Bu..... butyl

t-Bu ..... *tert*-butyl

B3LYP ..... 3-parameter hybrid Becke exchange/Lee-Yang-Parr correlation functional

C.....Celsius

calc'd..... calculated

Cbz .....carboxybenzyl

CD ..... circular dichroism

cm..... centimeters

d.....doublet

DCE.....dichloroethane

DCM .....dichloromethane

DFT .....density functional theory

DIBAL ..... diisobutylaluminum hydride

DMF ..... dimethylformamide

dr ..... diastereomeric ratio

δ ..... chemical shift in parts per million

° ..... degrees

ee ..... enantiomeric excess

er ..... enantiomeric ratio

Eq. ..... equation

equiv. ..... equivalents

ESI-MS ..... electrospray ionization mass spectrometry

Et ..... ethyl

EtOH ..... ethanol

FMO ..... frontier molecular orbital

g ..... grams

h ..... hours

H ..... hydrogen

HFIP ..... hexafluoroisopropanol

HOMO ..... highest occupied molecular orbital

HPLC ..... high purity liquid chromatography

Hz ..... hertz

I.D. ..... inner diameter

i-Pr ..... isopropyl

IR ..... infrared

J ..... coupling constant

J ..... joules

L ..... liters

LAH ..... lithium aluminum hydride

lit. ..... literature value

LUMO ..... lowest unoccupied molecular orbital

m ..... multiplet

m ..... meta

M ..... moles per liter

MCR ..... multicomponent reaction

Me ..... methyl

MeOH ..... methanol

mg ..... milligrams

MHz ..... megahertz

min ..... minutes

mL ..... milliliters

μL ..... microliters

mm ..... millimeters

mM ..... millimoles per liter

mmol ..... millimoles

mol ..... moles

MOM ..... methoxymethyl

M.S. ..... molecular sieves

μw ..... microwave

m/z ..... mass per charge ratio

nm ..... nanometers

NMP ..... *N*-methylpyrrolidine

o ..... ortho

p ..... para

Ph ..... phenyl

ppm ..... parts per million

q ..... quartet

RBF ..... round bottom flask

rr ..... regiomeric ratio

rt ..... room temperature

s ..... singlet

sec ..... seconds

t ..... triplet

t_r ..... retention time

THF ..... tetrahydrofuran

TLC ..... thin layer chromatography

TMS ..... trimethylsilyl

UPLC ..... ultra purity liquid chromatography

UV ..... ultraviolet

VANOL.....vaulted 2,2’-binaphthol

VAPOL .....vaulted 2,2’-biphenanthrol

vis.....visible

CHAPTER ONE. Asymmetric Allylboration of Acyl Cyanides

Introduction

Cyanohydrins are moieties that have found utility in synthesis due to their accessibility and facile transformation into different functional groups (Figure 1.1)[1–3]. Cyanohydrin **1.1** can be directly converted to α-hydroxy acid **1.2** through acid hydrolysis of the nitrile. Grignard addition to the nitrile followed by aqueous work-up provides α-hydroxy ketone **1.3**. The cyanohydrin can also be partially reduced to α-hydroxy aldehyde **1.4** with DIBAL, or fully reduced to β-amino alcohol **1.5** with LAH.

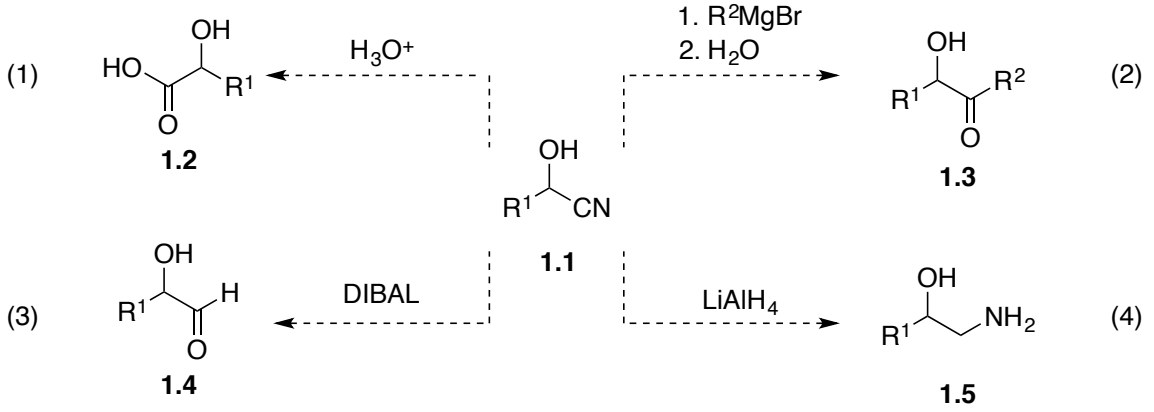


Figure 1.1. Functional group transformations of cyanohydrins

Cyanohydrins' most notable implementation in synthesis is the monosaccharide chain lengthening introduced by Kiliani in 1931, which later came to be known as the Kiliani-Fischer synthesis[4]. Varma and French reported on the mechanism of this process[5] with α-D-arabinose. Addition of NaCN to monosaccharide **1.6** provides a diastereomeric mixture of cyanohydrins **1.7** and **1.8** (Figure 1.2). Following lactonization and

subsequent reduction, monosaccharides **1.9**, D-glucose, and **1.10**, D-mannose, are obtained: the starting sugar chains extended by one carbon.

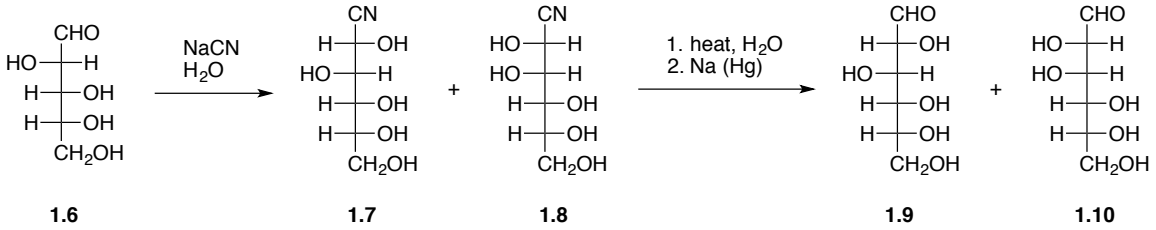


Figure 1.2. Kiliani-Fischer synthesis

The utility of this method has led to cyanohydrins' continued use in modern syntheses as building blocks. Of particular importance are ketone-derived cyanohydrins as precursors to quaternary centers. Such cyanohydrins can be used as synthons in complex syntheses of natural products and pharmaceuticals. Merck's process group led by Steven Weissman developed a manufacturing route to Raltegravir Potassium, an HIV integrase inhibitor, starting from acetone cyanohydrin. (Figure 1.3)[6].

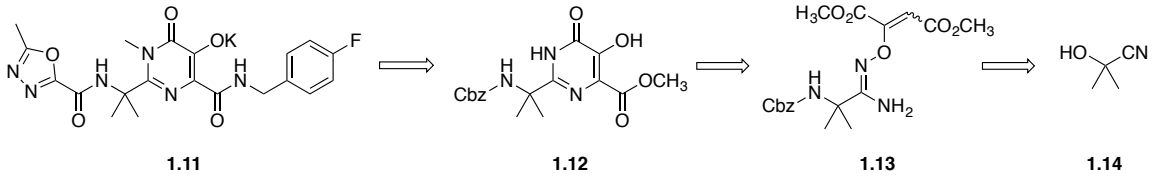


Figure 1.3. Neurokinin receptor antagonist accessed through an enantioenriched tertiary cyanohydrin

Utilizing an elegant synthetic strategy, Weissman converted cyanohydrin **1.14** to the oxime in 3 steps, followed by a Michael addition into dimethyl acetylenedicarboxylate (DMAD) to afford **1.13**. Further transformations produced hydroxypyrimidinone intermediate **1.12** and final protecting group manipulations and coupling reactions led to Raltegravir **1.11**. The process was effectively scaled up a multi-

hundred kilogram scale, and conversion of **1.12** to **1.11** was increased from 20% in the medicinal chemistry synthesis to 84%.

Cyanohydrins can be accessed through two different nucleophilic methods. The first and more common route is addition of cyanide to ketones and aldehydes with HCN or TMSCN. Alternatively, non-nitrile nucleophilic additions to acyl cyanides also afford cyanohydrins (Figure 1.4). In routes 1 and 2, there is a possibility of retro-CN additions, which lends to the instability of **1.16**. To date, only cyanosilylation reactions have been performed asymmetrically.

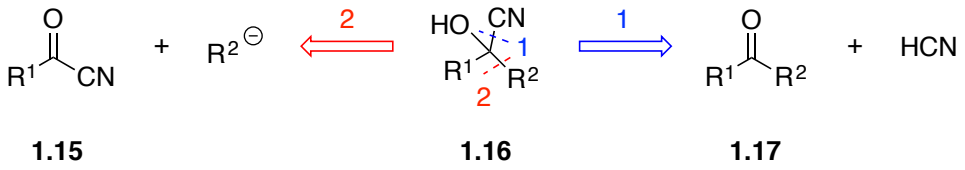
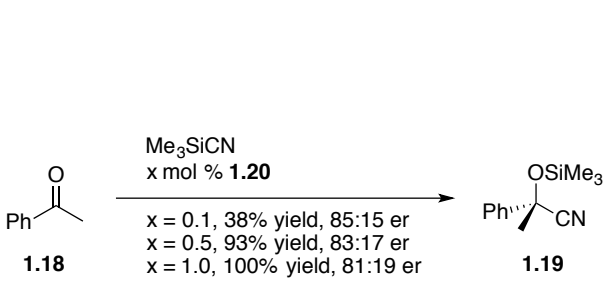


Figure 1.4. Synthesis of cyanohydrins

The use of titanium and chiral ligands to promote the synthesis cyanohydrins has been expansively studied. North reported a Ti-Salen catalyzed route to tertiary cyanohydrins (Figure 1.5)[7]. Using TMSCN as the nucleophilic nitrile source, they were able to isolate desired TMS-protected cyanohydrin **1.19**. North examined the catalyst loading at 0.1, 0.5, and 1 mol %. While the best selectivity was achieved at 0.1



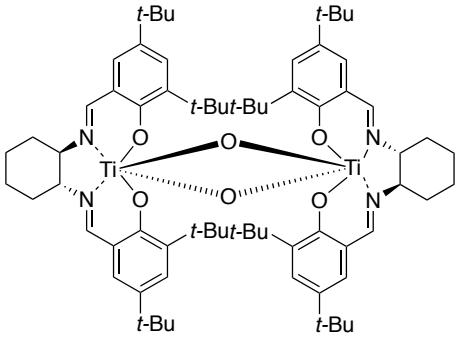


Figure 1.5. Ti-Salen catalyzed cyanohydrin synthesis

mol %, the yield suffered greatly at 38%. He obtained the product in quantitative yields with only 1 mol % catalyst loading, and only a slight loss of enantioselectivity (81:9 er). North's methodology offered the first transition metal catalyzed route to cyanohydrins *via* asymmetric addition of TMSCN to ketones.

Lewis basic ligands have also been shown to promote the asymmetric reaction. A route was published Shibasaki used a chiral phosphine oxide as the Lewis basic ligand to induce stereoselectivity[8]. At 10 mol % loading of Ti(O*i*-Pr)$_4$ and chiral ligand **1.21**, the cyanosilylation transformation of acetophenone **1.18** afforded **1.19** in 85% yield and 96:4 er (Figure 1.6). This method was applicable to aromatic, aliphatic, and α,β-unsaturated ketones, providing the corresponding cyanohydrins in up to 92% yield and up to 96:4 er.

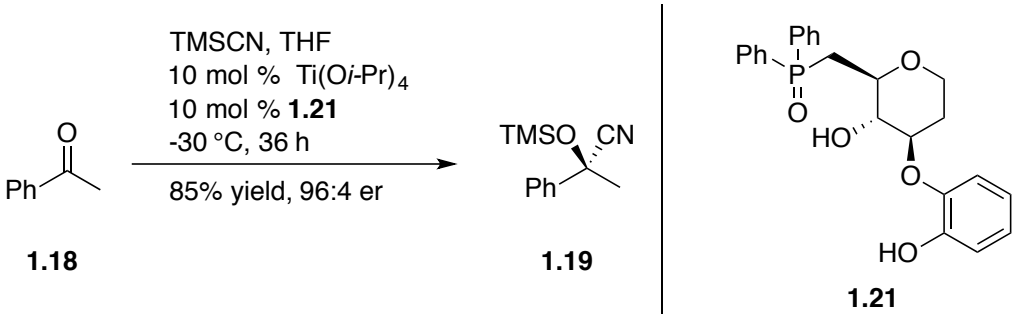
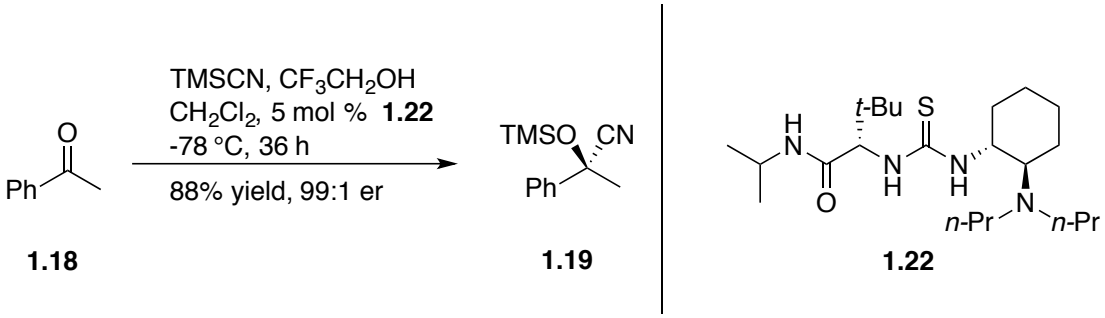


Figure 1.6. Titanium-chiral phosphine oxide cyanosilylation of acetophenone

The same system can also be catalyzed with thioureas. Jacobsen reported on this process and was able to access the chiral cyanohydrin in 88% yield and 99:1 er (Figure 1.7)[9]. In the presence of trifluoroethanol, DCM, and 5 mol % catalyst, TMS-cyanohydrin

1.19 was obtained in 36 hours at -78 °C.



1.18 **1.19** **1.22**

Figure 1.7. Thiourea catalyzed cyanohydrin synthesis

Jacobsen performed both NMR and kinetic studies to better understand the catalyst role in the transformation. Relying on *in situ* generation of HCN with TMSCN and CF_3CH_2OH, ^{13}C NMR analysis was used to confirm its formation. Both GC and IR were utilized to determine the bifunctional role of the thiourea catalyst as well as to determine the rate- and selectivity-determining steps of the transformation.

The examples shown above all rely on the addition of TMSCN to a carbonyl. A challenge of these methodologies is the combined volatility and toxicity of cyanide reagents. A way around this is to use nucleophile sources other than cyanide. As such, investigations into nucleophilic addition to acyl cyanides have gained popularity in the synthetic community. Kraus reported an allylation of commercially available acetyl cyanide with allyltrimethylsilane to generate the homoallylic cyanohydrin[10]. Acyl cyanide **1.23** was converted to cyanohydrin **1.25** in 89% yield (Figure 1.8). This transformation was achieved under $TiCl_4$ Lewis acid catalysis upon nucleophilic addition of allyl-TMS **1.24**.

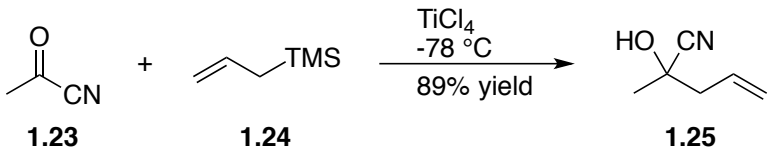


Figure 1.8. Synthesis of homoallylic cyanohydrins with allyltrimethylsilane

Clerici utilized an *in situ* reduction of benzoyl cyanide in the presence of acetone to obtain mixed 1,2-diols (Figure 1.9)[11]. Benzoyl cyanide **1.26** was coupled with acetone to afford α-hydroxy cyanohydrin **1.28** in 54% yield after 1 hour. This method relies on weakly reducing $TiCl_3$ to generate a stabilized capto-dative radical of the acyl cyanide, which then adds into the aldehyde or ketone coupling partner. Upon slow addition of $TiCl_3$ in acetic acid rather than acetone, Clerici also saw the dimerization of benzoyl cyanide in 75% yield.

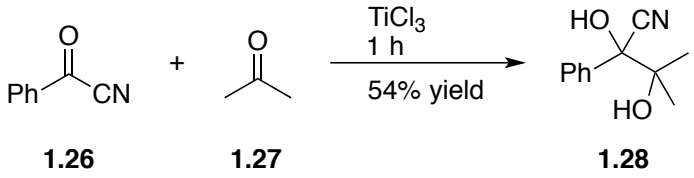
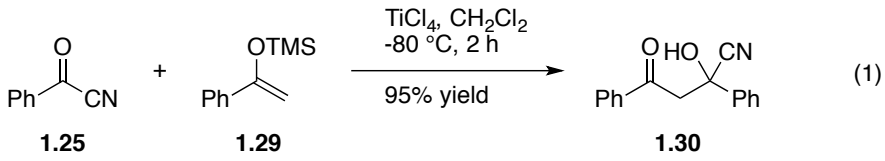


Figure 1.9. Titanium trichloride catalyzed synthesis of α-hydroxy cyanohydrins

As part of the route to access Porphobilinogen, Neier's group showed a Mukaiyama Aldol-type reaction between a silyl enol ether and an acyl cyanide to generate a β-keto cyanohydrin in high yield[12,13]. In a model reaction to determine the scope of the Mukaiyama aldol reaction, they reported the addition of silyl enol ether **1.29**

to benzoyl cyanide to obtain cyanohydrin **1.30** in 97% isolated yield (Figure 1.10, Eq. 1).



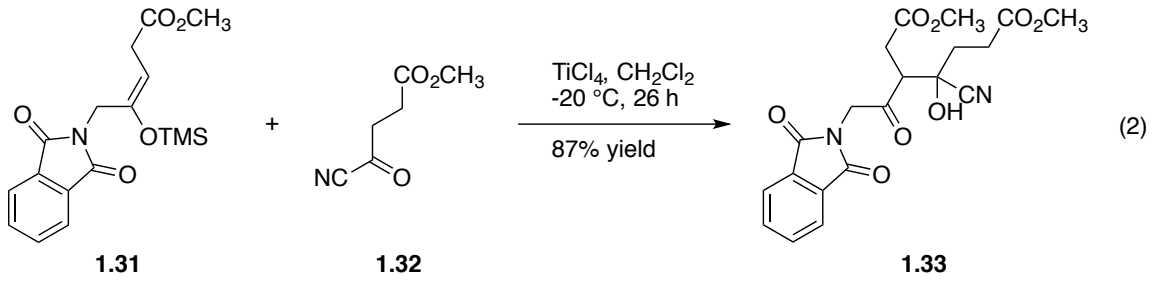
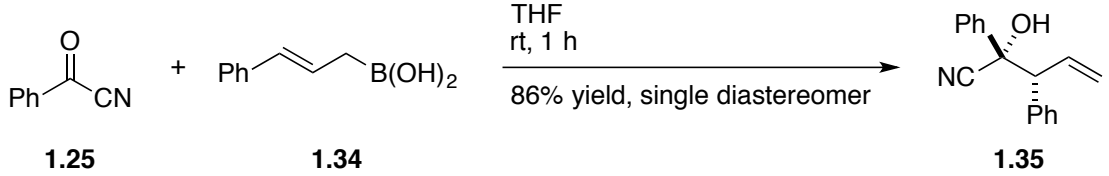


Figure 1.10. Synthesis of β-keto cyanohydrins *via* a Mukaiyama Aldol reaction

Optimization of these conditions for their substrates led to increasing both the temperature to -20 °C and the reaction time to 26 hours (Eq. 2). This led to an isolated yield of key intermediate **1.33** in 87% yield starting from acyl cyanide **1.32** and enol ether **1.31**. This was then carried through to the desired Porphobilinogen synthon in a 25% overall yield, in 4 steps from the silyl enol ether precursor.

Szabó and co-workers found they could access adjacent stereocenters *via* an allylboration of benzoyl cyanide to the cyanohydrin[14]. Benzoyl cyanide was treated with boronic acid **1.34** in THF for 1 hour to generate cyanohydrin **1.35** in 86% yield (Figure 1.11). The product was isolated as a single diastereomer through a *syn*-selective mechanism. They were also able to apply this to acetyl cyanide to access the corresponding product in 72% yield. However, due to the decreased steric bias between

the nitrile and a methyl group, as opposed to a phenyl group, the cyanohydrin was only obtained in a 9:1 dr.



1.25 **1.34** **1.35**

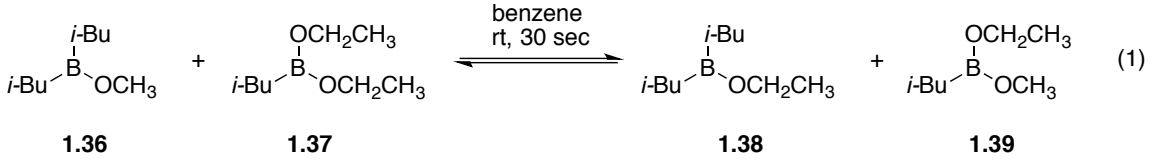
Figure 1.11. Allylboration synthesis of cyanohydrins

This transformation by Szabó was reported shortly after we developed an allylboration of acyl cyanides based on our asymmetric boronate addition methodologies. Nucleophilic allylborations of ketones and acyl imines, along with crotylborations and allenylborations of ketones have been reported by the Schaus lab[15–18]. We envisioned a straightforward application of our methodologies to provide access to enantiopure cyanohydrins with a focus on carbon-carbon bond formation at the acyl cyanide.

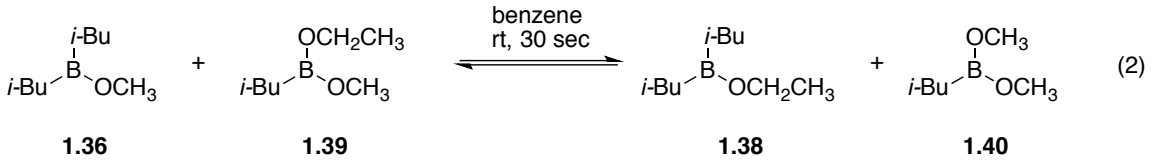
Background

Boronate Exchange Methodology

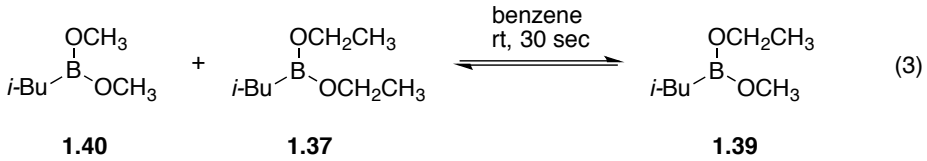
Nucleophilic boronate addition is an effective method for forming new carbon-carbon bonds. Much work has been done in this field to optimize and expand the application of these transformations. Of particular interest is the asymmetric addition of boronates to ketones and aldehydes, which capitalizes on facile exchange of the boronate ligands. In 1962, McCusker reported on the ease of this ligand exchange[19]. He found that at room temperature, he was able to see alkoxy ligand exchange through proton NMR analysis. When examining dialkylalkoxyborane **1.36** and alkyldialkoxyborane **1.37**, he observed new boranes **1.38** and **1.39** (Figure 1.12, Eq. 1). He also



1.36 **1.37** **1.38** **1.39**



1.36 **1.39** **1.38** **1.40**



1.40 **1.37** **1.39**

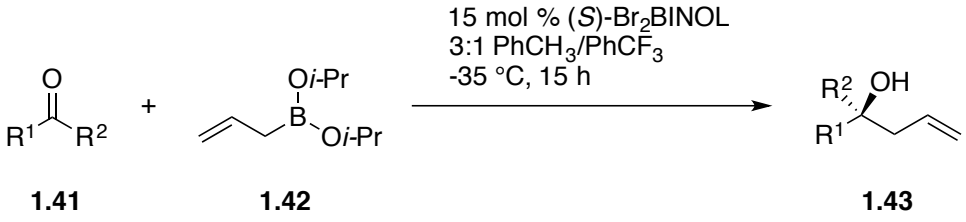
Figure 1.12. Boronate ligand exchange study

looked into the exchange of dialkylalkoxyborane **1.36** with the new alkyldialkoxyborane **1.39** that was formed (Eq. 2). Again, a statistical mixture of the expected exchange products **1.38** and **1.40** was observed. Finally, the exchange of *iso*-butyl boronates **1.40** and **1.37** were studied, and mixed boronate ester **1.39** was observed as the only product (Eq. 3). Notably, these exchanges had reached a stable equilibrium in 30 seconds at room temperature, indicating that the process is both favored and rapid.

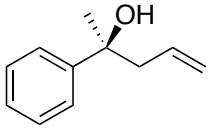
Asymmetric Allylboration of Ketones and Acyl Imines

With this information in hand, we developed asymmetric nucleophilic allylboration reactions that take advantage of boronate ligand exchange. Dr. Sha Lou and Dr. Philip Moquist reported an asymmetric allylboration of ketones catalyzed by chiral biphenols[17]. After screening chiral diol catalysts, solvents, and temperatures with acetophenone, optimal conditions were found to be 15 mol % loading of (*S*)-Br_2BINOL in a 3:1 solvent mixture of toluene and trifluorotoluene, at -35 °C. Under these conditions, 15 ketones were screened and found to behave satisfactorily in the reaction (Figure 1.13). Acetophenone gave desired homoallylic alcohol **1.44** in good yield and selectivity (83%, 97:3 er). A *meta*-substituted aromatic ketone provided corresponding product **1.46** and 89% yield, and 95.5:4.5 er, while *para*-substitution, **1.45**, produced higher selectivity (99.5:0.5 er) with comparable yield. Heteroaromatic acetylthiophene also participated well in the reaction, leading to alcohol **1.49** in high yield and 97:3 er. Cyclic ketones were also investigated and produced **1.50** in 88% yield and 96.5:3.5 er. Non-aromatic ketone 1-acetylcyclohexene gave homoallylic alcohol **1.51** in 91% yield

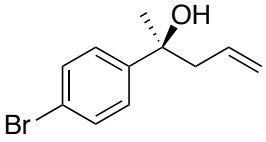
and 96.5:3.5 er, with no evidence of the alternative conjugate addition product. Finally, an alkynyl aromatic ketone gave **1.52** in 93% yield and 95:5 er.



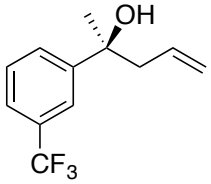
1.41 **1.42** **1.43**



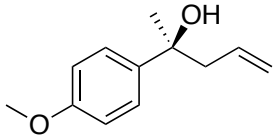
1.44, 83% yield, 97:3 er



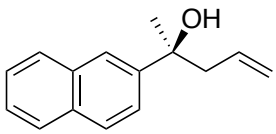
1.45, 86% yield, 99.5:0.5 er



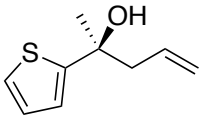
1.46, 89% yield, 95.5:4.5 er



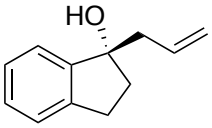
1.47, 83% yield, 99.5:0.5 er



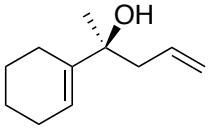
1.48, 81% yield, 96.5:3.5 er



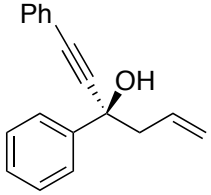
1.49, 87% yield, 97:3 er



1.50, 88% yield, 96.5:3.5 er



1.51, 91% yield, 96.5:3.5 er



1.52, 93% yield, 95:5 er

Figure 1.13. Selected substrates for the asymmetric allylboration of ketones

Asymmetric crotylborations were also investigated. Under the same reaction conditions as the allylations, *syn*- and *anti*- crotylation products were obtained (Figure 1.14, Eqs. 1 and 2). *E*-Crotylboronate **1.53** provided *anti*-alcohol **1.54** in 72% yield, 98:2

dr, and 99:1 er, while *Z*-crotylboronate **1.56** led to the *syn* product (**1.57**) in 75% yield, 99:1 dr, and 98.5:1.5 er. These major diastereomers are the expected products for the given boronates, as predicted by a Zimmerman-Traxler transition state model (**1.55** and **1.58**).

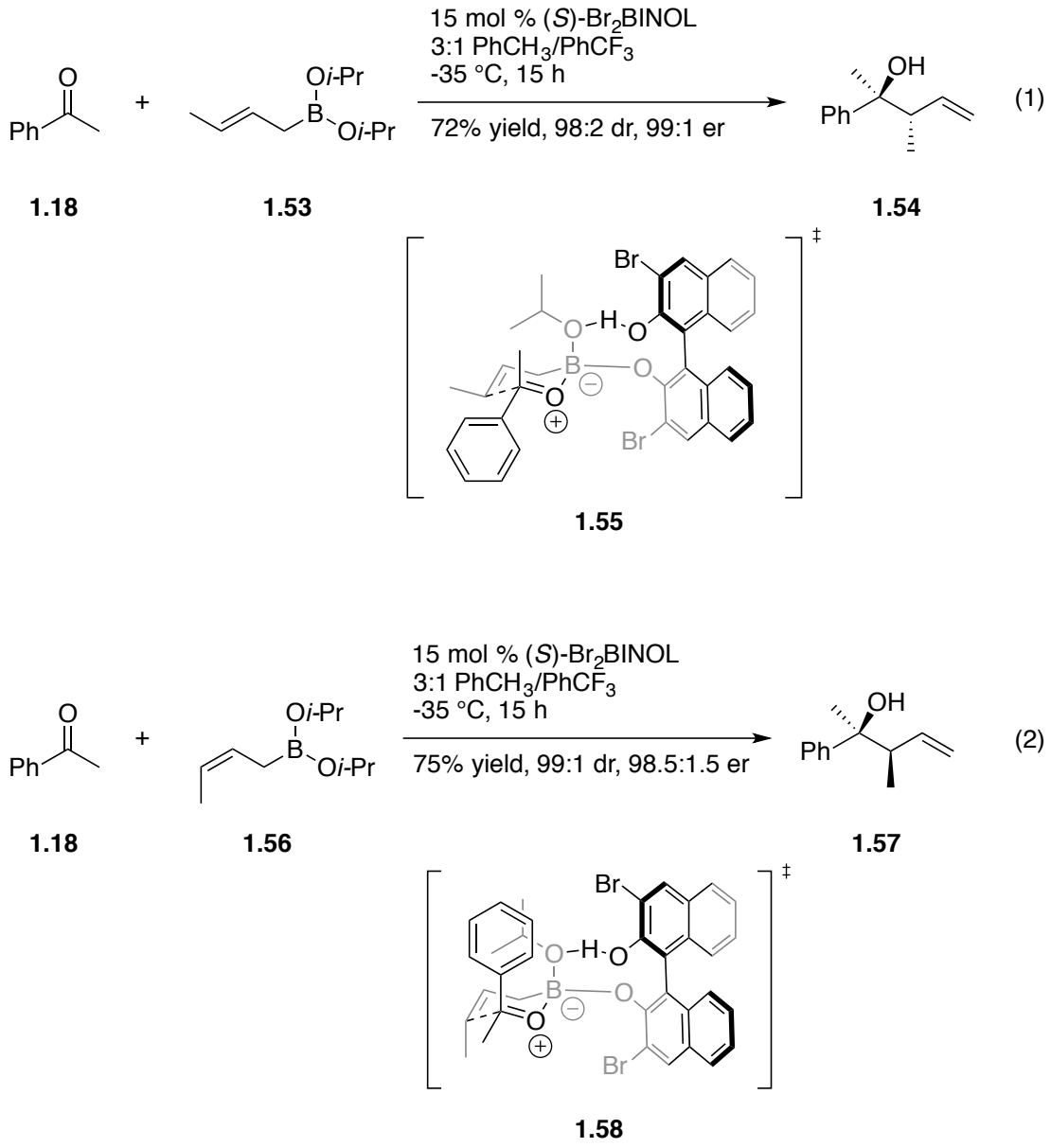


Figure 1.14. Asymmetric crotylborations of acetophenone

In an effort to lower the catalyst loading of this allylboration, Dr. David Barnett and Dr. Philip Moquist, formerly of the Schaus laboratory, performed mechanism studies on the reaction[15]. Upon in-depth kinetic, NMR, and mass spectrometry studies, a more hydrolytically stable cyclic boronate was employed in the reaction and the catalyst loading dropped to 2 mol %. Nine of the same ketones, as well as seven new ones, were examined under the new conditions (Figure 1.15). All 9 of the ketones being re-studied saw an increase in yield, and either an increase or retention of enantioselectivity. Parent ketone acetophenone gave **1.44** in 96% yield and 99:1 er, an enhancement in both yield and selectivity compared to the previous method. Among new ketones, *ortho*-bromo substituted acetophenone provided **1.61** in 95% yield and 98:2 er. The reaction to provide β-keto ester derived product **1.62** proceeded with 98% yield and 99:1 er, and showed only the ketone reacted as the electrophile.

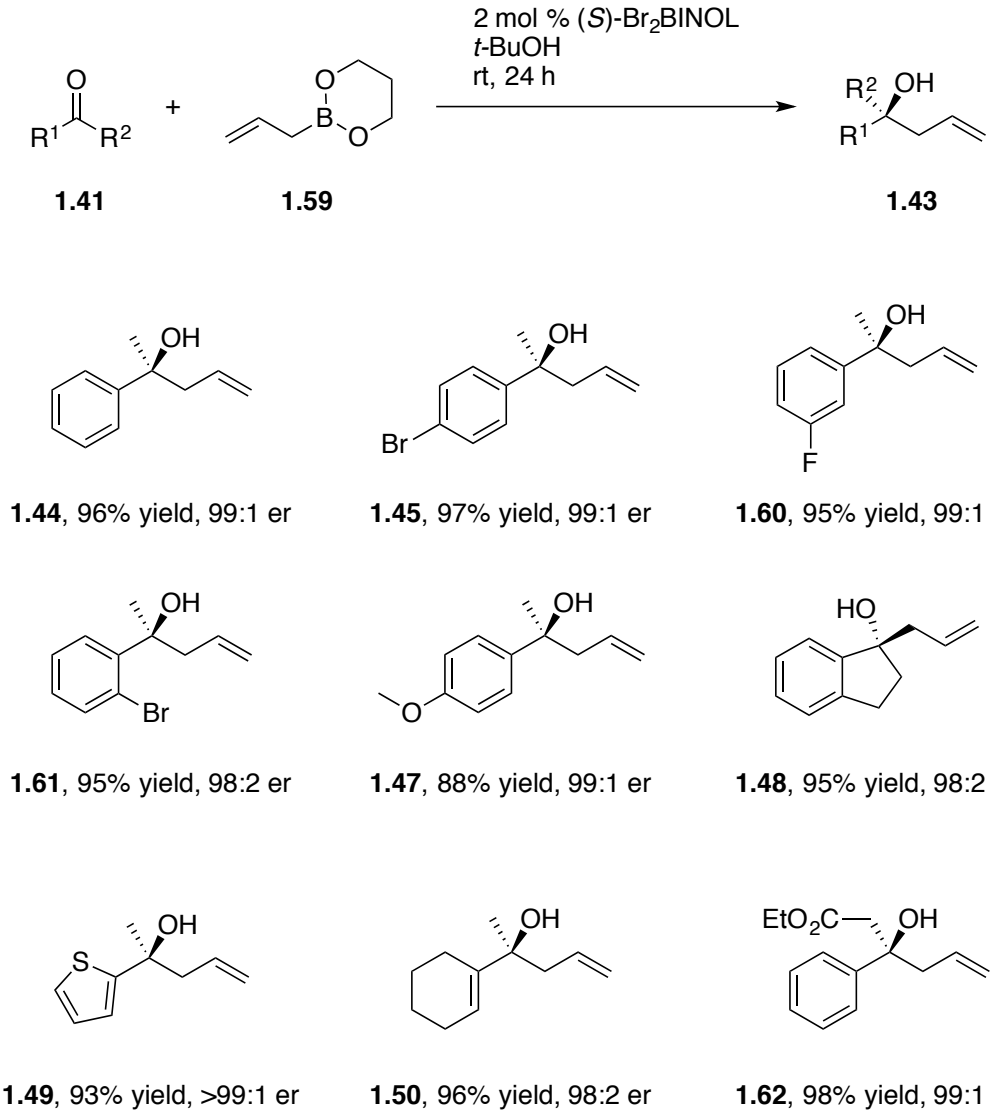


Figure 1.15. Selected substrates for improved allylboration of ketones

Similarly, the crotylations also performed well under reduced catalyst loading conditions (Figure 1.16). At 4 mol % (*S*)-Br_2BINOL, the *E*-crotylation gave 96% yield, 97:3 dr, and 99:1 er, while the *Z*-crotylation gave 94% yield, 98:2 dr, and 97:3 er. In addition to changing the diisopropylboronate to the dioxaborinane, this reaction was run under neat conditions with 2.0 equivalents of *t*-BuOH as an additive. We believe that the

t-BuOH helps activate the boronate towards exchange with the diol catalyst through coordination to boron's empty *p*-orbital.

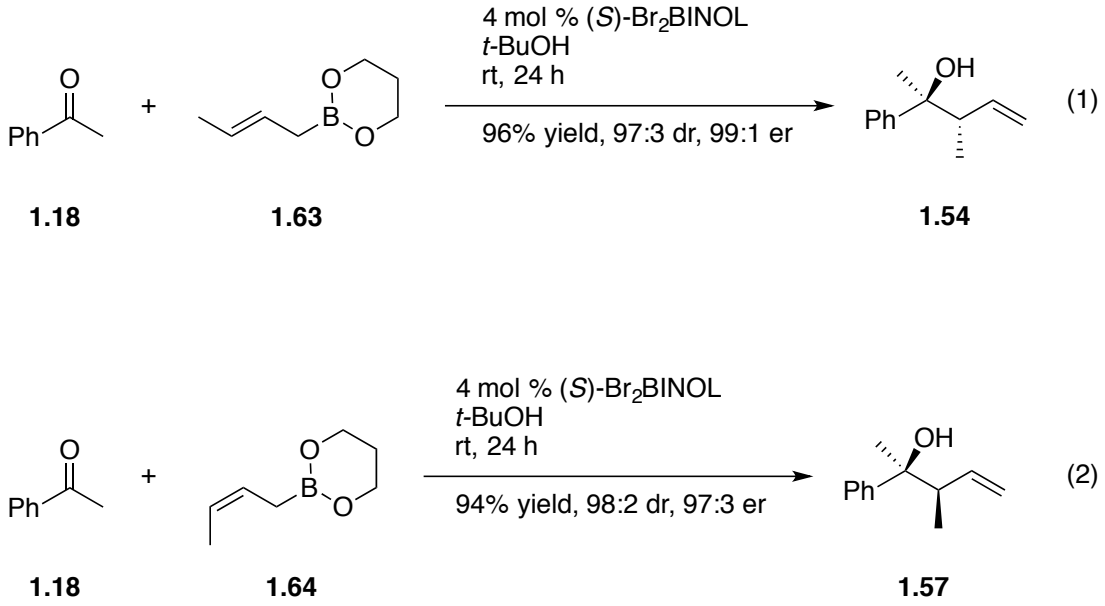


Figure 1.16. Improved crotylboration of acetophenone

Dr. Lou and Dr. Moquist also reported an allylboration of acyl imines shortly after developing their ketone allylation[18]. With 15 mol % (*S*)-Ph_2BINOL, the homoallylic amine products were obtained in good yields and selectivities (Figure 1.17). The reaction was examined with different *N*-benzylidene derivatives, and found to tolerate both aromatic and aliphatic imine substrates. Electron-neutral *N*-benzylidene benzamide reacted to give **1.67** in 87% yield and 99:1 er. Electron-rich substitutions on the aromatic ring, such as 4-methoxy, also worked well in the reaction (**1.68**, 85% yield, 95:5 er). Electron-deficient substituents were evaluated both electronically and sterically. Substitutions at the *para*, *meta*, and *ortho* positions were all tolerated in the reaction (**1.69** – **1.71**). Finally, the aliphatic cyclohexyl benzylidene derivative proceeded to corresponding homoallylic amine **1.72** in 80% yield with 98:2 er. Varying the *N*-

substitution to incorporate different acyl groups was also shown to be amenable to the methodology. Lou and Moquist were able to apply this methodology to the synthesis of a potent HIV-I inhibitor, demonstrating its utility[20,21].

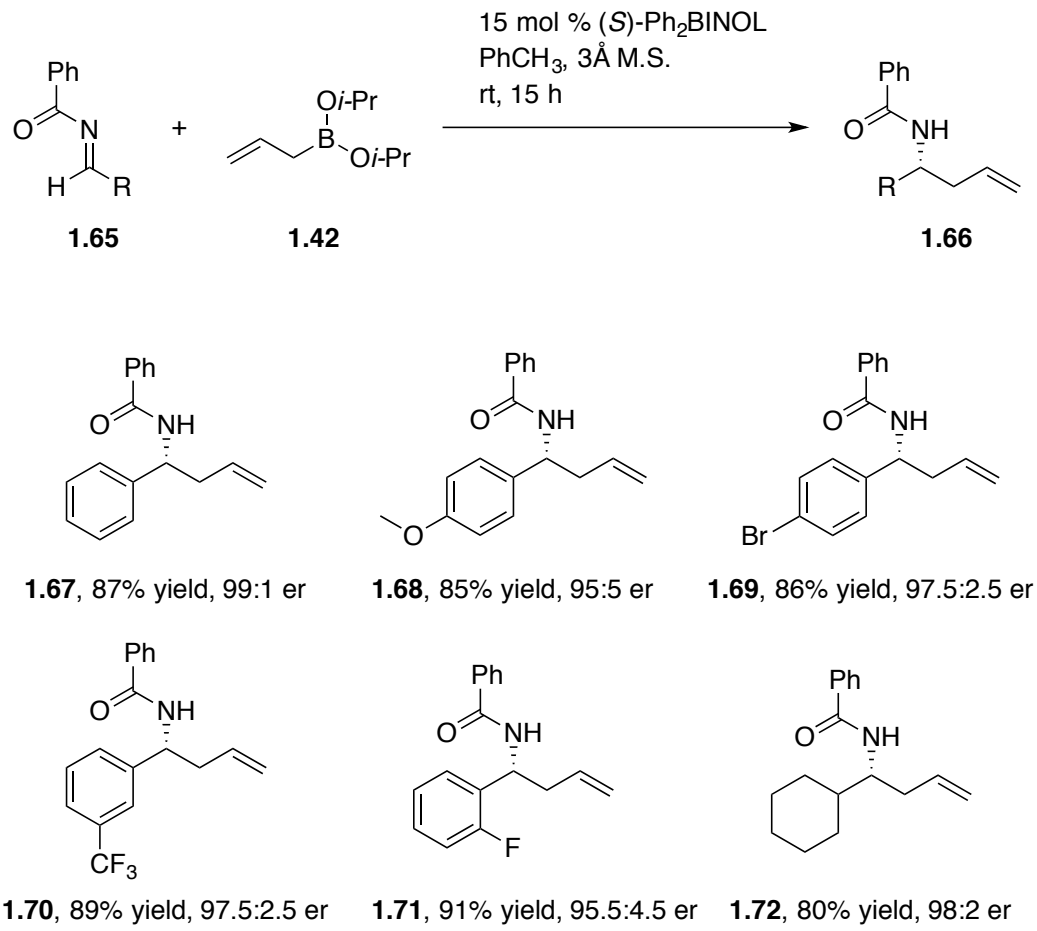


Figure 1.17. Selected substrate scope for the allylation of acyl imines

Asymmetric Allenylboration of Ketones

In addition to being good electrophiles for allyl boronates, ketones also readily accept allenyl boronate nucleophiles. Expanding the scope of the asymmetric boronate exchange methodology studied in the Schaus lab, Dr. Barnett developed an asymmetric allenylboration of ketones to access propargyl alcohols[16]. Under microwave irradiation

and neat conditions, the propargylation of acetophenone was achieved in 85% yield and 97:3 er (Figure 1.18). This methodology proved to be applicable to aromatic, heteroaromatic, aliphatic, and α,β-unsaturated ketones, as well as β-keto esters.

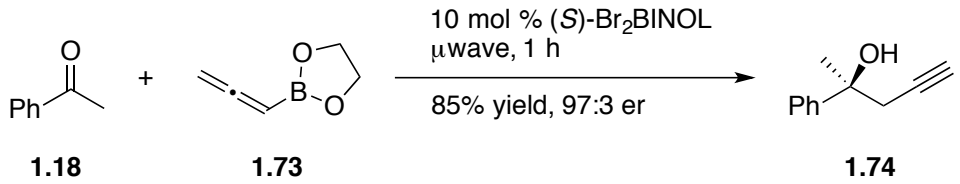


Figure 1.18. Asymmetric allenylboration of acetophenone

A diastereoselective allenylboration was also accomplished using allenyl boronates substituted at the terminal olefin, providing the *syn* product as the major diastereomer. It is believed that this transformation proceeds through an open transition state, unlike that of the allylation. Using racemic methyl-allenyl boronate, the *syn* propargyl alcohol was obtained as the major diastereomer in 86:14 er. The transition state that leads to the major diastereomer exhibits the least disfavored gauche interactions. This method illustrates a broadened scope for chiral diol catalyzed nucleophilic boronate reactions.

Based on our knowledge of boronate exchange methodology and the general electrophilicity of acyl cyanides[22], we set out to develop an enantioselective synthesis of tertiary homoallylic cyanohydrins *via* nucleophilic boronate addition to acyl cyanides. We envisioned a direct application of our ketone allylboration conditions to the new system, and began investigations with *B*-allyl-1,3,2-dioxaborinane and (*S*)-Br_2BINOL. Herein, we report a facile route to enantioenriched cyanohydrins.

Results and Discussion

Asymmetric Allylboration of Acyl Cyanides

A direct transfer of the allylboration methodology to a system using acyl cyanides in the place of ketones was first examined. Commercially available benzoyl cyanide was substituted for acetophenone in the previously optimized reaction conditions, with *B*-allyl-1,3,2-dioxaborinane and *t*-BuOH (Figure 1.19). To our delight, this modification worked seamlessly. At room temperature after 16 hours, the desired cyanohydrin was obtained in 85% yield and 98:2 er.

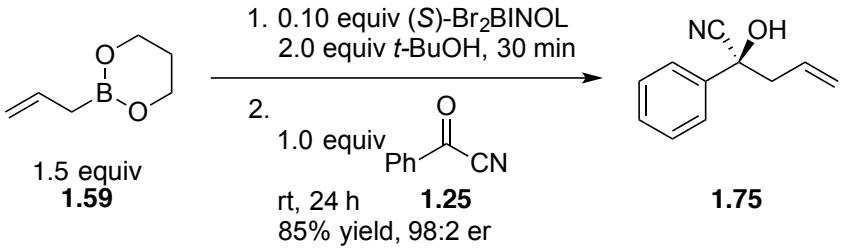
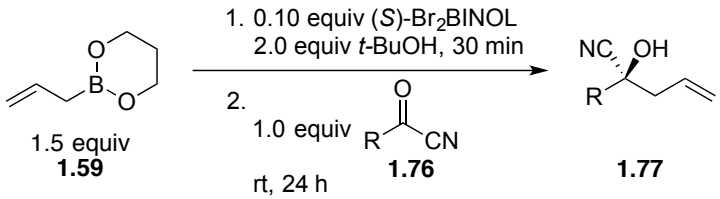


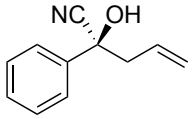
Figure 1.19. Asymmetric allylboration of benzoyl cyanide

Substrate Scope

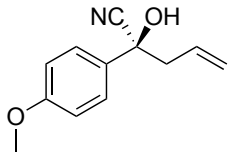
With an optimized parent reaction, we then shifted focus to exploring the substrate scope of the reaction (Figure 1.20). In that context, we learned that the reaction proceeds with aromatic acyl cyanides very well. Electron-donating *p*-methoxy substitution gave **1.79** in 94% yield and 99:1 er. Likewise, electron-rich 3,4-methylenedioxybenzoyl cyanide provided **1.83** in 92% yield and 99:1 er. Electron-deficient substrates performed equally well in the reaction. Substituting a *p*-nitro group led to isolation of **1.89** in 70% yield and 96:4 er, while addition of a *p*-trifluoromethyl

group gave cyanohydrin **1.90** in 80% yield with 97:3 er. More sterically hindered acyl cyanide substrates were also screened. We found that while *meta*-tolyl acyl cyanide proceeded with only slightly compromised selectivity when compared to the *para*-substitution (95:5 and 99:1 er, respectively), the *ortho*-tolyl afforded cyanohydrin **1.81** with 95:5 er, but in only 67% isolated yield.

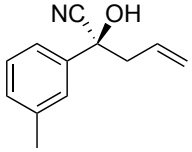




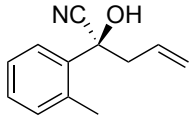
1.78, 85% yield, 98:2 er



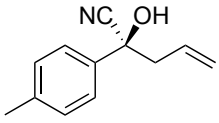
1.79, 94% yield, 99:1 er



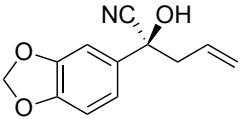
1.80, 86% yield, 95:5 er



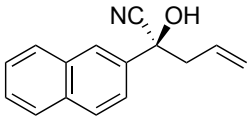
1.81, 67% yield, 95:5 er



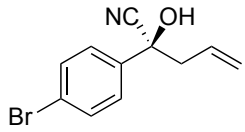
1.82, 89% yield, 99:1 er



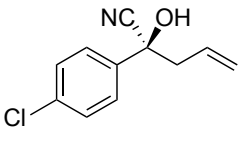
1.83, 92% yield, 99:1 er



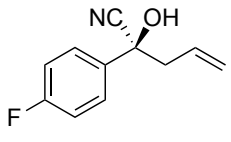
1.84, 97% yield, 95:5 er



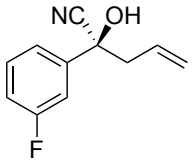
1.85, 91% yield, 98:2 er



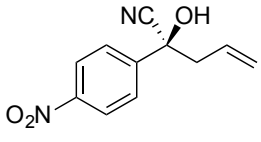
1.86, 82% yield, 97:3 er



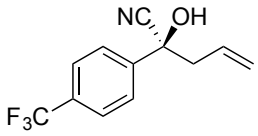
1.87, 69% yield, 96:4 er



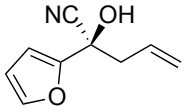
1.88, 70% yield, 93:7 er



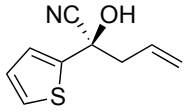
1.89, 70% yield, 96:4 er



1.90, 80% yield, 97:3 er



1.91, 35% yield, 85:15 er



1.92, 50% yield, 50:50 er

Figure 1.20. Substrate scope of the asymmetric allylboration of acyl cyanides

Interestingly, heteroaromatic acyl cyanides did not perform as expected. Furan-derived cyanohydrin **1.89** was obtained in a low 35% yield and 85:15 er, and thiophene-derived product **1.90** was isolated in 50% yield as a racemic mixture. This decrease in reactivity and stereoinduction was quite surprising, especially considering how well acetylthiophene behaved in the ketone allylation (Figure 1.15, **1.49**). The decrease in reactivity could be due to the highly electron donating properties of the heteroatoms, making the carbonyl less electrophilic through π-donation of the lone pairs. The compromised selectivities could be attributed to a disruption in the chiral transition state, as the completely racemic results for **1.105** indicate either poor facial selectivity for the acyl cyanide, or lack of participation of the chiral diol catalyst in the nucleophilic addition. Additionally, these products are the only two that exhibit immediate decomposition into the corresponding ketones. This retro-CN addition forming the ketone, and subsequent possible addition to reform the cyanohydrin could also attribute to the low enantioselectivities for these substrates.

Proposed Reaction Mechanism

Once the substrate scope had been identified, a mechanism similar to that demonstrated in our previous work was proposed (Figure 1.21). The *t*-butanol coordinates to the empty *p*-orbital of boronate **1.59**, facilitating a single exchange with the chiral diol catalyst, **1.93**. After single exchange, the lone pair of the oxygen from benzoyl cyanide **1.25** donates in to coordinate to the boron's empty *p*-orbital, forming boron-ate complex **1.95**. Ate complex **1.95** then delivers the allyl group to the activated

carbonyl carbon *via* a closed transition state to give intermediate **1.96**. Hydrolysis of the boron-oxygen bonds yields the desired product and regenerates catalyst **1.93**.

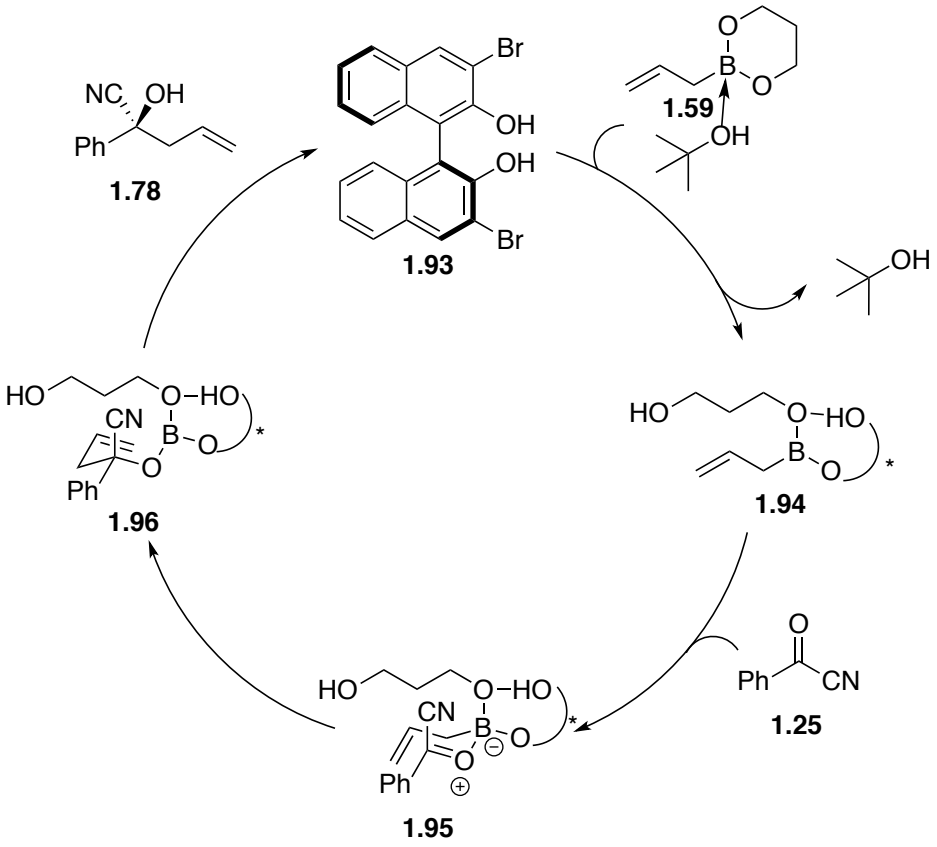
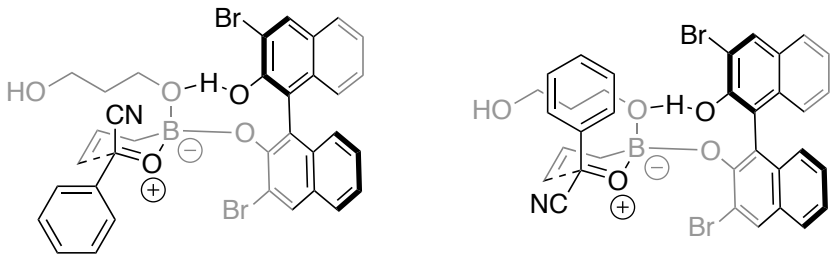


Figure 1.21. Proposed catalytic cycle

Absolute Stereochemistry Assignment

With a proposed catalytic cycle in hand, we turned our attention to a model for reaction stereoselectivity (Figure 1.22). We envision a closed, Zimmerman-Traxler transition state model, similar to that of our ketone allylation work. Through a chair-like transition state, addition to the *re*-face of benzoyl cyanide would be favored, resulting in the (*S*)-enantiomer product being formed. This positions the nitrile of the acyl cyanide in

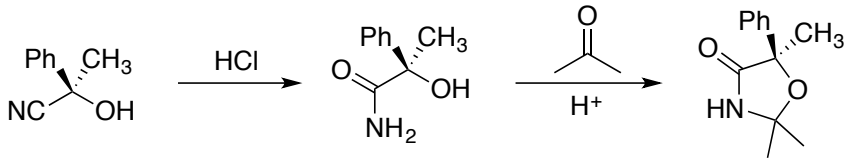
a pseudo-axial position and the aryl group pseudo-equatorial. Based on relative A-strain values for the nitrile, 0.24, and phenyl group, 2.8, this conformation should be the preferred transition state[23,24].



1.97 **1.98**

Figure 1.22. Proposed transition state model

In order to determine the absolute stereochemistry of our products, we hoped to compare the optical rotation of **1.78** with literature reported values. Unfortunately, only the Schrader group to date has published an asymmetric synthesis of *ent*-**1.78**, and no $[\alpha]_D$ values are reported[25,26]. Schrader instead used chiral NMR experiments with TADDOL to determine er, and conversion to enantiomerically pure oxazolidinone **1.101** to determine absolute configuration by comparison to the literature (Figure 1.23).



1.99 **1.100** **1.101**

Figure 1.23. Conversion of acetophenone cyanohydrin to oxazolidinone

Relying on chiral NMR studies to determine the enantiomer of our products, we turned to examples published by Louzao and co-workers in 2006 and 2009[27,28]. In their work, they report the synthesis of the methoxyphenylacetic ester of aldehyde and ketone

cyanohydrins. From these esters, shifts in proton and carbon NMR peaks can be analyzed to determine which enantiomer of cyanohydrin we have made. Importantly, Louzao notes that for α-aromatic cyanohydrins, the key $\Delta\delta^{RS}$ values for identifying the cyanohydrin enantiomer are those from the aromatic group. That is to say, the relative upfield or downfield shift of aromatic signals from the (*R*)-MPA ester to the (*S*)-MPA ester indicates the absolute stereochemistry of the ketone cyanohydrin.

We envisioned forming both the (*R*)- and (*S*)-MPA esters of **1.82** and following Louzao's steps for determining absolute stereochemistry (Figure 1.24). Based on calculations done by Louzao, in conjunction with CD and low-temperature NMR, the conformational equilibria of the MPA esters can be summarized as a single conformer significant for the NMR studies (**1.102** and **1.103**).

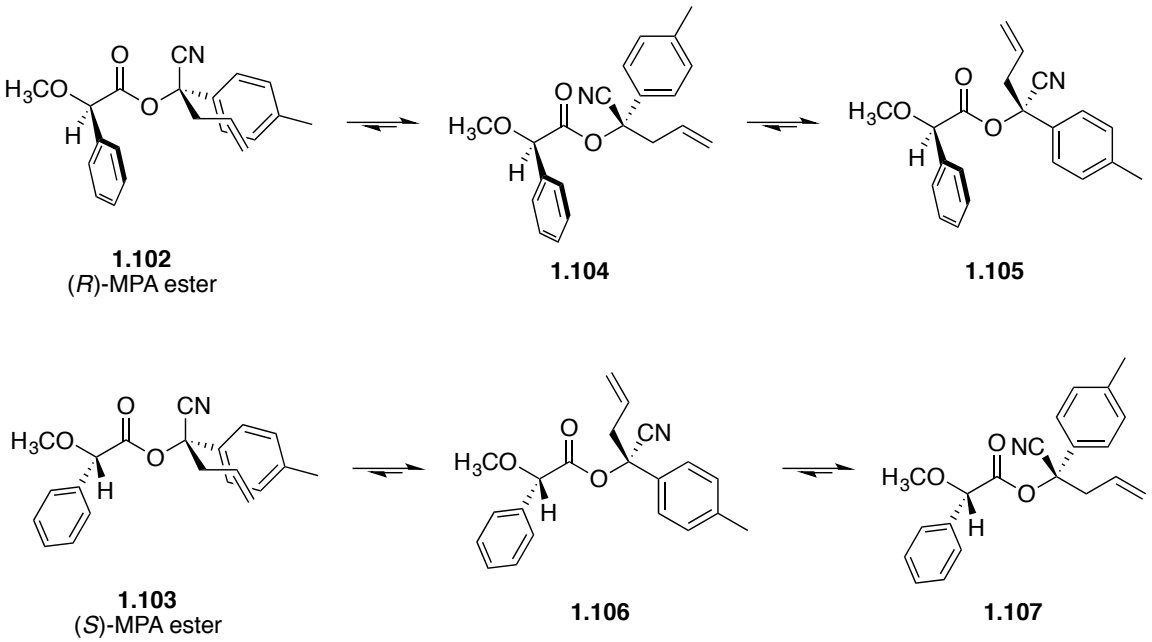


Figure 1.24. NMR significant conformers and conformational equilibria of mandelate esters

With our proposed absolute configuration of (*S*) based on our transition state model, we would expect to see an upfield shift in the aromatic doublets and methyl protons based on their location with respect to the (*R*)- and (*S*)-MPA phenyl group shielding cones. Alternatively, if we made the (*R*)-enantiomer of our product, we would anticipate the opposite trend.

The esterification reactions between cyanohydrin **1.82** and chiral derivatizing agents (*R*)- and (*S*)-MPA were carried out in dry DCM with EDC and catalytic DMAP. The resultant esters were extracted, dried, and analyzed by proton NMR at 500 MHz (Figure 1.25). The identifying aromatic signals were compared between spectra, and a relative upfield shift of 0.20 and 0.23 ppm from the (*R*)-ester to the (*S*)-ester of aromatic protons was observed. Additionally, the signal for the tolyl methyl protons exhibited an upfield shift of 0.03 ppm. This indicates that the *p*-methylphenyl group lies in the shielding cone of the MPA phenyl group in the (*S*)-ester. This observation is in agreement with the absolute stereochemistry of an (*S*)-cyanohydrin (Table 1.1).

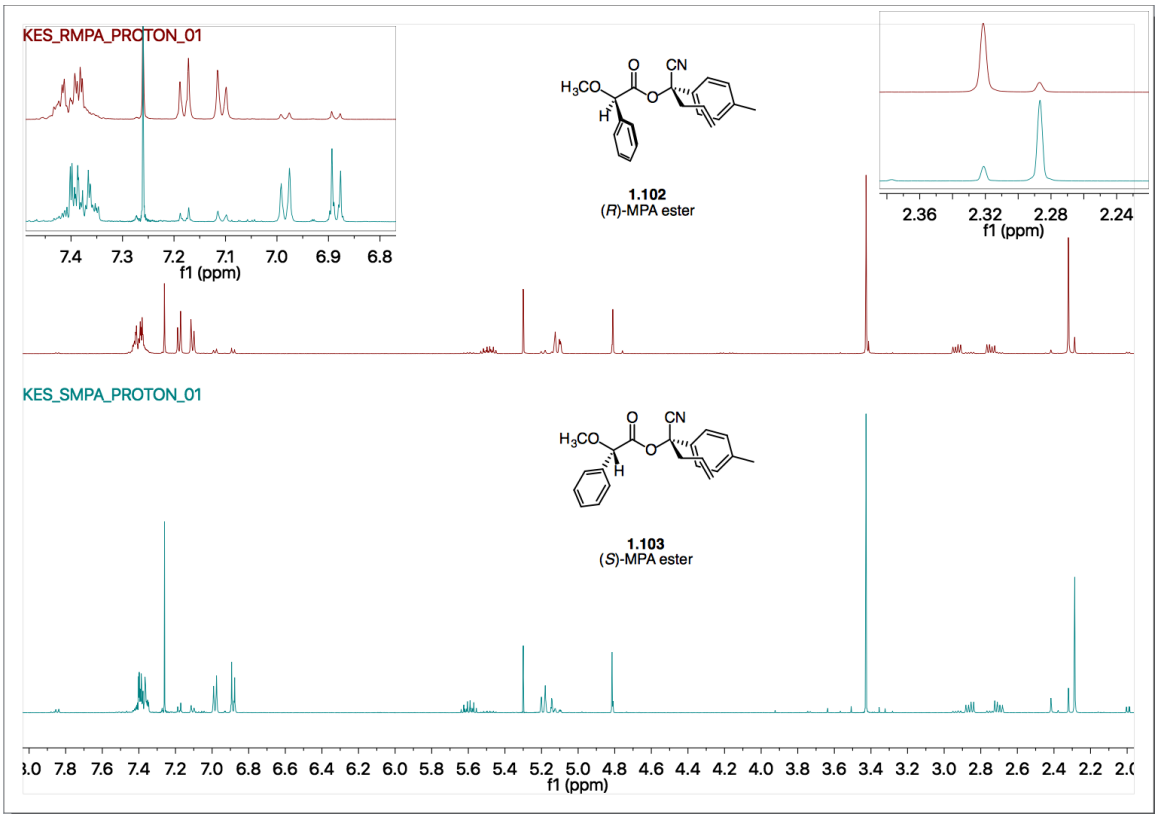


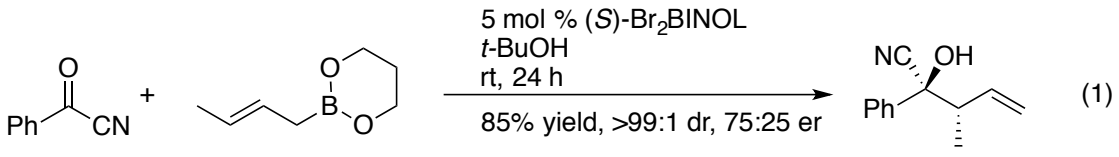
Figure 1.25. Chiral NMR determination of absolute stereochemistry at 500 MHz

Proton	(*R*)-MPA ester δ (ppm)	(*S*)-MPA ester δ (ppm)	$\Delta\delta^{RS}$ (ppm)
1	7.40	7.38	+0.02
2	7.18	6.98	+0.20
3	7.11	6.88	+0.23
4	5.49	5.60	-0.11
5	5.13	5.18	-0.05
6	5.10	5.18	-0.08
7	4.81	4.81	0.0
8	3.43	3.43	0.0
9	2.93	2.86	+0.07
10	2.75	2.70	+0.05
11	2.32	2.29	+0.03

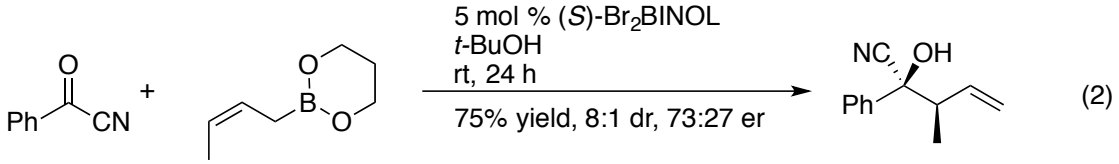
Table 1.1. Proton shifts at 500 MHz and $\Delta\delta^{RS}$ of (*R*)- and (*S*)-MPA esters for the assignment of absolute stereochemistry

Crotylboration of Benzoyl Cyanide

Upon completion of the allylation, we began initial investigations into the crotylboration of benzoyl cyanide (Figure 1.26). At 5 mol % catalyst loading of (*S*)-Br_2BINOL, *anti*-cyanohydrin **1.108** was obtained from reaction with **1.63** in 85% yield as a single diastereomer with 75:25 er. Likewise, *syn*-cyanohydrin **1.109** was isolated in 75% yield, with an 8:1 dr and 73:27 er, *via* crotylation with **1.64**. While the yields of these reactions were satisfactory, the low enantiomeric ratios (er's) of both products and low dr of **1.109** were not desired. Based on these results, we sought to optimize the selectivities of the transformation.



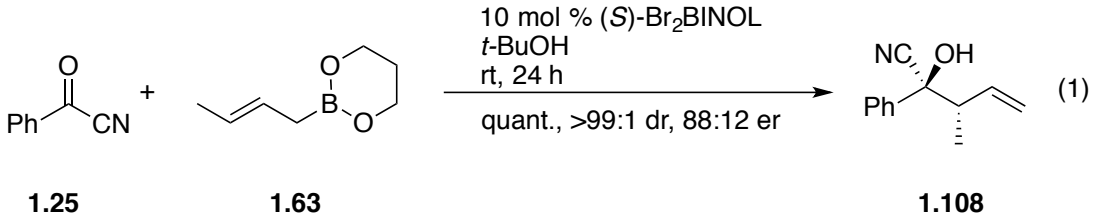
1.25 **1.63** **1.108**



1.25 **1.64** **1.109**

Figure 1.26. Preliminary results for the crotylboration of benzoyl cyanide

To start optimizing the reaction, we first looked at increasing the catalyst loading (Figure 1.27). We found that increasing the amount of (*S*)-Br_2BINOL from 5 mol % to



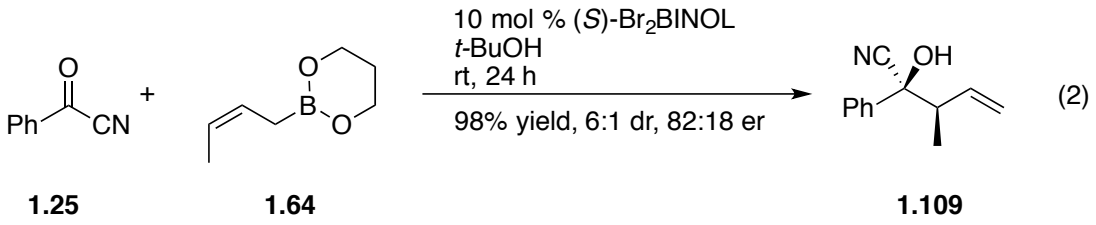


Figure 1.27. Crotylboration of benzoyl cyanide with 10 mol% catalyst loading

10 mol % led to an increase in both yield and selectivity. The *anti*-cyanohydrin was accessed in quantitative yields again as a single diastereomer, with an er of 88:12. *Syn*-cyanohydrin was obtained in high yield (98%) with an increased er of 82:12 and a dr of 6:1. While an improvement from the initial reactions, these results are still not optimized for enantioselectivity.

In an effort to maximize the enantiomeric ratio for these reactions, we looked into changing the chiral diol catalyst. We imagined that incorporating larger substituents at the 3,3'-positions on BINOL would help to increase the selectivity of our reaction. To test this hypothesis, the crotylborations were studied using 10 mol % (*R*)-Ph_2BINOL that was readily available in the lab (Figure 1.28). With this new, bulkier catalyst, the *anti*-

and *syn*-products were obtained as opposite enantiomers, accounting for the use of the

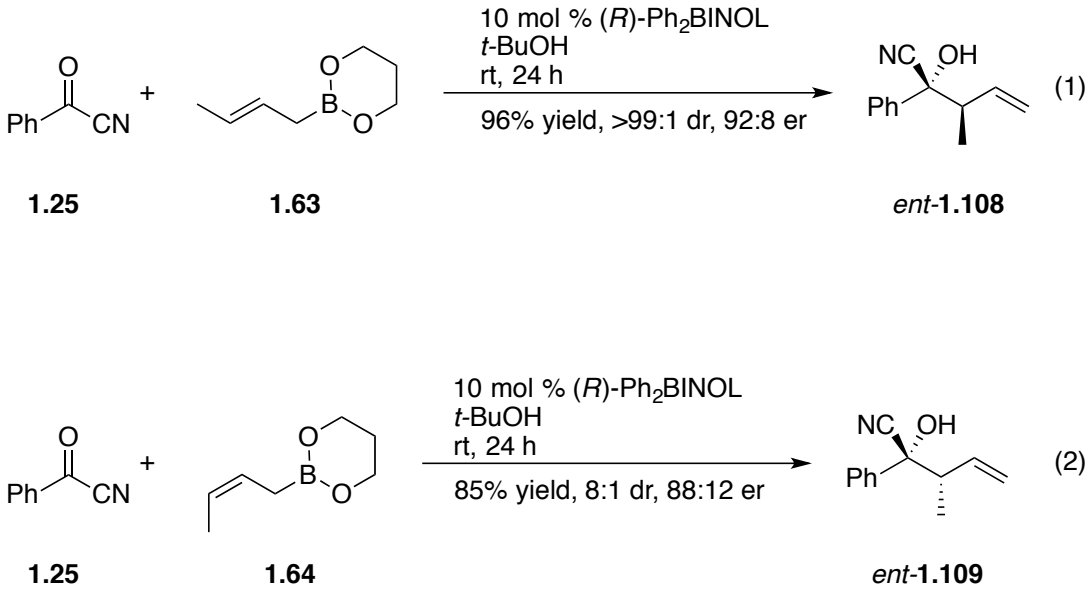
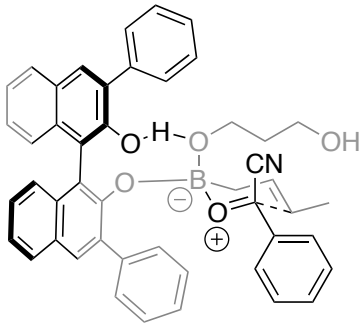


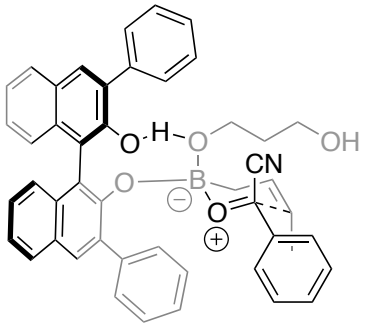
Figure 1.28. Optimized crotylboration of benzoyl cyanide

(*R*)-catalyst. Compound *ent*-**1.108** was isolated in 96% yield, as a single diastereomer, and with 92:8 er. Boronate **1.64** gave *ent*-**1.109** in 88:12 er, 8:1 dr, and 85% isolated yield under the new conditions.

This diastereoselective reaction is expected to react *via* a closed Zimmerman-Traxler transition state, similar to that of the allylation process (Figure 1.29). Based on relative cyclohexane A-strain values, the nitrile would be positioned in the pseudo-axial position, and the phenyl in the pseudo-equatorial position. These orientations in the transition state with *E*-crotylboronate would lead to the *anti*-product as demonstrated in model **1.110**. Similarly, reaction with *Z*-crotylboronate would proceed through transition state **1.111**, leading to the *syn*-product. These models are in agreement with our previously proposed allylation and crotylation transition states.



1.110



1.111

Figure 1.29. Transition state model for the croylboration of benzoyl cyanide with (*R*)-Ph_2BINOL

Conclusion

In conclusion, we efficiently accessed tertiary cyanohydrins enantioselectively *via* a carbon/boronate nucleophile. The transformation was performed in solvent-free conditions for most substrates, as the boronate volume was enough to solubilize the remaining substrates. A mechanism for this reaction was proposed based on our previous ketone allylboration methodology, and predicted absolute stereochemistry determined by a Zimmerman-Traxler transition state. Chiral NMR studies with the methoxyphenylacetic ester of the cyanohydrins gives insight into the stereocenter formed through upfield and downfield shifts of chemical resonances.

The methodology was extended to include a diastereoselective crotylboration of acyl cyanides, and was optimized by the use of a bulkier BINOL catalyst. The relative stereochemistry is proposed based on the same Zimmerman-Traxler transition state as the allylation, and corresponds to the ketone crotylboration transition state. Due to the nitrile's significantly lower cyclohexyl A-strain value when compared to the phenyl group, its location in the pseudo-axial position is much more favored over the phenyl.

To the best of our knowledge, this methodology represents the first catalytic asymmetric allylboration of acyl cyanides to synthesize homoallylic cyanohydrins. The method's broad utility is represented through its application to electron-rich, electron-neutral, and electron-deficient substrates, all products of which were obtained with good yields and selectivities.

Experimental Information

General Information

All ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Unity Plus 500 MHz spectrophotometer at ambient temperature in $CDCl_3$. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Low resolution mass spectrometry data was obtained on an Agilent LC/MSD VL system by electrospray (ESI) flow injection analysis in the positive mode. Mobile phases were water and acetonitrile with 0.1% formic acid. The MS settings were: voltage = 3000V, fragmentor = 70 and chamber temperature = 350 °C. UPLC-MS analysis was performed on a C18 column (1.7mm, 2.1 X 50 mm) with CH_3CN:H_2O gradient as eluent with UV, ELSD and electrospray ionization (ESI) positive ion detection. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]_D$ (concentration in grams/100mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC System with a diode array detector. Chiral columns include Chiralcel® OD (Chiral Technologies Inc., 25 cm x 4.6 mm I.D.), Chiralpak® AD-H (Chiral Technologies Inc., 25 cm x 4.6 mm I.D.), Chiralpak® IA (Chiral Technologies Inc., 24 cm x 4.6 cm I.D.) and (*R,R*)-Whelk-O (Regis® Technologies Inc., 25 cm x 4.6 mm I.D.).

*General Procedure for the Preparation of Allyl Boronate **1.59***

This compound was prepared according to the literature[15]. An oven-dried 500-mL round bottom flask was charged with a stir bar and to it was added anhydrous diethyl ether (100 mL). The flask was then flushed with argon and to it was added trimethylborate (17 mL, 150 mmol) *via* syringe with stirring. The flask was then cooled to -78 °C on a dry ice/acetone bath and kept under Ar. To the flask was added dropwise 1.0 M allyl magnesium bromide in diethyl ether (150 mL, 150 mmol) *via* addition funnel over 30 minutes. The reaction was stirred for 20 minutes and warmed to room temperature. The reaction was then cooled to 0 °C, and 228 mL of an aqueous HCl solution (2 M) was added slowly through an addition funnel. The aqueous layer was washed three times with 50 mL diethyl ether. The organic layers were combined and dried over $MgSO_4$. The solution was then filtered through a cotton plug into a new 500-mL RBF and concentrated on the rotovap to 200 mL. To the solution of boronic acid in ether was added 1,3-propanediol (11mL, 150 mmol) and 75 g $MgSO_4$. The solution was allowed to stir for 16 hours at room temperature under argon. The solution was filtered through a sintered glass funnel and the $MgSO_4$ was washed twice with ~75mL ether. The solution was concentrated on the rotovap (water bath not exceeding 25 °C). To the resultant liquid was added 150mL pentane and the solution was stored in the -80 °C freezer for 1.5 hours. The flask was removed from the freezer and warmed to room temperature. Excess 1,3-propanediol crashed out as a viscous liquid and was removed *via* pipette. The solution was then filtered through celite and concentrated on the rotovap, with water bath not exceeding 25 °C. The product was then distilled *via* Kugelrohr to

yield the desired boronate (15.5 g, 82% yield). The spectral data was in agreement with reported values.[29]

General Procedure for the Preparation of (S)-Br_2BINOL

This compound was prepared according to the literature[30], with a modification for the final deprotection step. To an oven-dried 500 mL RBF charged with a stir bar was added NaH (2.92 g, 60% in oil, 73.0 mmol) and dry THF (150 mL). The suspension was cooled to 0 °C and the flask affixed with an argon balloon. To the suspension was added a solution of (*S*)-1,1'-binaphthol (9.5 g, 33.2 mmol) and THF (50 mL) slowly *via* syringe. The solution was allowed to stir at 0 °C for 1 hour and was then warmed to room temperature for 15 minutes. The solution was then re-cooled to 0 °C and then to it was added chloromethyl methyl ether (5.54 mL, 73.0 mmol) *via* syringe. The reaction was then warmed to room temperature and allowed to stir for 4.5 hours. The reaction was then quenched slowly with aqueous NH_4Cl (50 mL) and concentrated on the rotovap. The residue was dissolved in DCM (50 mL) and the organic phase separated. The aqueous phase was extracted twice more with DCM (50 mL), and the organic layers were pooled, washed with brine (50 mL), dried over Na_2SO_4, and concentrated on the rotovap. The crude material was recrystallized from DCM/hexanes to give a white crystalline product ((*S*)-MOM_2-BINOL, quantitative). An oven-dried 250mL RBF was charged with a stir bar and to it was added (*S*)-MOM_2-BINOL (2.5 g, 6.68 mmol) and diethyl ether (110 mL). Once the solid had dissolved (about 5min), to the reaction was added *n*-BuLi (12.5 mL, 1.6 M in hexane, 20.03 mmol) via syringe. The reaction was then allowed to stir at room temperature for 3 hours. To the flask was then added THF (75 mL) and it

was allowed to stir an additional hour at room temperature under Ar. The reaction was then cooled to 0 °C and to it was added 1,2-dibromo-1,1,2,2-tetrachloroethane (8.3 g, 25.5 mmol) in one portion. The reaction was then warmed back to room temperature for 30 min under Ar. The reaction was then quenched with saturated aqueous NH_4Cl (100 mL). The two phases were separated and the aqueous layer washed twice with diethyl ether (75 mL). The pooled organic layers were dried over Na_2SO_4, concentrated on the rotovap, and dried under vacuum. Crude (*S*)-Br_2-MOM_2-BINOL material brought forward for deprotection. The crude material (3.55 g, 6.68 mmol) in a 250 mL RBF, was dissolved in DCM (100 mL) and MeOH (50 mL). To it was added 2M HCl in ether (10 mL, 20 mmol) and the solution was heated to reflux for 4 hours. The reaction was then cooled to room temperature and to it was added saturated aqueous $NaHCO_3$ (75 mL). The neutralized solution was then placed on the rotovap to remove the organic layer. The residue was then dissolved in DCM (50 mL) and the organic phase separated. The aqueous layer was then washed twice more with DCM (50 mL), the organic layers combined, dried over Na_2SO_4, and concentrated on the rotovap. The crude product was then recrystallized from DCM/hexanes to afford the product as a yellow powder (2.61 g, 88% over 2 steps). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.25 (s, 2H), 7.81 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.39 (ddd, *J* = 8.3, 6.8, 1.1 Hz, 2H), 7.31 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 2H), 7.10 (dd, *J* = 8.3, 1.2 Hz, 2H), 5.55 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 148.17, 132.92, 129.89, 127.74, 127.56, 125.03, 124.78, 114.77, 112.40.

General Procedure for the Preparation of Racemic Homoallylic Cyanohydrins

To an oven dried reaction tube charged with a stir bar was added 2,2'-biphenol (0.019 g, 0.10 mmol), *tert*-butanol (0.19 mL, 2.0 mmol), and *B*-allyl-1,3,2-dioxaborinane (0.189 g, 1.5 mmol). The tube was purged with argon, and the reaction allowed to stir at room temperature for 30 minutes. To the reaction was then added benzoyl cyanide (0.131 g, 1.0 mmol) and it was allowed to stir for 16 hours at room temperature. The crude reaction mixture was dry loaded onto silica, purified *via* flash chromatography, elution with DCM, and used for racemic HPLC traces.

General Procedure for the Preparation of Chiral Homoallylic Cyanohydrins

To an oven dried reaction tube charged with a stir bar was added (*S*)-Br_2BINOL (0.044 g, 0.10 mmol), *tert*-butanol (0.19 mL, 2.0 mmol), and *B*-allyl-1,3,2-dioxaborinane (0.189 g, 1.5 mmol). The tube was purged with argon, and the reaction allowed to stir at room temperature for 30 minutes. To the reaction was then added benzoyl cyanide (0.131 g, 1.0 mmol) and it was allowed to stir for 16 hours at room temperature. The crude reaction mixture was dry loaded onto silica and purified *via* flash chromatography, elution with DCM. The product was isolated as a pale yellow oil (0.135 g, 85% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.59 (m, 2H), 7.47 – 7.38 (overlap, 3H), 5.88 (dddd, *J* = 17.0, 10.2, 8.2, 6.4 Hz, 1H), 5.36 (dddd, *J* = 10.2, 1.7, 0.9, 0.9 Hz, 1H), 5.31 (dddd, *J* = 17.0, 1.7, 1.5, 1.2 1H), 2.93 (s, OH), 2.83 (dddd, *J* = 14.0, 6.4, 1.5, 0.9 Hz, 1H), 2.72 (dddd, *J* = 14.0, 8.2, 1.2, 0.9 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ

139.23, 130.45, 129.36, 128.99, 125.06, 122.61, 120.46, 73.42, 48.37. **ESI⁻-MS** *m/z* calc'd for $[C_{11}H_{11}NO\text{-}H]^-$ 172.08, found 172.05.

Analytical Data

(S)-2-hydroxy-2-(4-methoxyphenyl)pent-4-enenitrile ***(1.79)***

This compound was prepared according to the general procedure using 4-methoxybenzoyl cyanide (0.16 g, 1.0 mmol) to afford to product as an oil (0.190 g, 94%). **er** = 99:1. $\mathbf{[\alpha]_D}$ = -3.8° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.86 (dddd, *J* = 17.0, 10.2, 8.2, 6.4 Hz, 1H), 5.34 (dddd, *J* = 10.2, 1.6, 1.1, 1.0 Hz, 1H), 5.29 (dddd, *J* = 17.0, 1.6, 1.2, 1.2 Hz, 1H), 3.83 (s, 3H), 2.88 (s, OH), 2.80 (dddd, *J* = 13.9, 6.4, 1.2, 1.1 Hz, 1H), 2.72 (dddd, *J* = 13.9, 8.2, 1.2, 1.0 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 160.24, 131.26, 130.57, 126.45, 122.33, 120.56, 114.22, 73.13, 55.49, 48.17. **ESI⁻-MS** *m/z* calc'd for $[C_{12}H_{13}NO_2\text{-}H]^-$ 202.09, found 202.13.

(S)-2-hydroxy-2-(m-tolyl)pent-4-enenitrile ***(1.80)***

This compound was prepared according to the general procedure using *m*-toluoyl cyanide (0.14 g, 1.0 mmol) to afford to product as an oil (0.161 g, 86%). **er** = 95:5. $\mathbf{[\alpha]_D}$ = -2.6° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.40 – 7.35 (overlap, 2H), 7.31 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 5.87 (dddd, *J* = 16.9, 10.2, 8.2, 6.5 Hz, 2H), 5.35 (dddd, *J* = 10.2, 1.7, 1.0, 0.9 Hz, 1H), 5.30 (dddd, *J* = 16.9, 1.7, 1.3, 1.2 Hz, 1H), 3.00 (s, OH), 2.80 (dddd, *J* = 14.0, 6.5, 1.3, 0.9 Hz, 1H), 2.71 (dddd, *J* = 14.0, 8.2,

1.2, 1.0 Hz, 1H), 2.40 (s, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 139.18, 138.89, 130.57, 130.11, 128.90, 125.65, 122.53, 122.10, 120.53, 73.42, 48.33, 21.65. **ESI$^-$-MS** *m/z* calc'd for $[C_{12}H_{13}NO\text{-}H]^-$ 186.10, found.

*(S)-2-hydroxy-2-(o-tolyl)pent-4-enenitrile **(1.81)***

This compound was prepared according to the general procedure using *o*-toluoyl cyanide (0.14 g, 1.0 mmol) to afford to product as an oil (0.125 g, 67%). **er** = 95:5. $[\alpha]_D$ = -5.1° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.28 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.25 – 7.21 (overlap, 2H), 5.96 (dddd, *J* = 17.0, 10.2, 8.4, 6.4 Hz, 1H), 5.41 (dddd, *J* = 10.2, 1.6, 1.0, 0.9 Hz, 1H), 5.35 (dddd, *J* = 17.0, 1.6, 1.3, 1.3 Hz, 1H), 3.00 (dddd, *J* = 14.2, 6.4, 1.3, 1.0 Hz, 1H), 2.97 (s, OH), 2.75 (dddd, *J* = 14.2, 8.4, 1.3, 0.9 Hz, 1H), 2.61 (s, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 136.00, 135.53, 132.91, 130.61, 129.24, 126.38, 125.79, 122.94, 120.42, 72.54, 45.33, 20.98. **ESI$^-$-MS** *m/z* calc'd for $[C_{12}H_{13}NO\text{-}H]^-$ 186.10, found 186.06.

*(S)-2-hydroxy-2-(p-tolyl)pent-4-enenitrile **(1.82)***

This compound was prepared according to the general procedure using *p*-toluoyl cyanide (0.14 g, 1.0 mmol) to afford to product as an oil (0.167 g, 89%). **er** = 99:1. $[\alpha]_D$ = -10.8° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 5.87 (dddd, *J* = 16.9, 10.2, 8.2, 6.5 Hz, 1H), 5.34 (dddd, *J* = 10.2, 1.6, 1.2, 1.0 Hz, 1H), 5.29 (dddd, *J* = 16.9, 1.6, 1.4, 1.2 Hz, 1H), 2.87 (s, OH), 2.80 (dddd, *J* = 14.0, 6.5, 1.4, 1.2 Hz, 1H), 2.71 (dddd, *J* = 14.0, 8.2, 1.2, 1.0 Hz, 1H), 2.38 (s, 3H). **^{13}C**

NMR (125 MHz, Chloroform-*d*) δ 139.35, 136.33, 130.58, 129.63, 124.99, 122.42, 120.56, 73.37, 48.25, 21.26. **ESI⁻-MS** *m/z* calc'd for $[C_{12}H_{13}NO\text{-}H]^-$ 186.10, found 185.99.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxypent-4-enenitrile ***(1.83)***

This compound was prepared according to the general procedure using piperonyloyl cyanide (0.18 g, 1.0 mmol) to afford to product as an oil (0.200 g, 92%). **er** = 99:1. $\mathbf{[\alpha]_D}$ = +1.3° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.08 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.04 (dd, *J* = 2.0, 0.4 Hz, 1H), 6.83 (dd, *J* = 8.1, 0.4 Hz, 1H), 6.01 (s, 2H), 5.85 (dddd, *J* = 17.0, 10.2, 8.2, 6.5 Hz, 1H), 5.35 (dddd, *J* = 10.2, 1.6, 1.1, 0.9 Hz, 1H), 5.29 (dddd, *J* = 17.0, 1.6, 1.4, 1.3 Hz, 1H), 2.98 (s, OH), 2.78 (dddd, *J* = 13.9, 6.5, 1.4, 1.1 Hz, 2H), 2.69 (dddd, *J* = 13.9, 8.2, 1.3, 0.9 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 148.40, 148.29, 133.14, 130.44, 122.53, 120.46, 118.95, 108.37, 105.74, 101.70, 73.20, 48.31. **ESI⁻-MS** *m/z* calc'd for $[C_{12}H_{11}NO_3\text{-}H]^-$ 216.07, found 216.06.

(S)-2-hydroxy-2-(naphthalen-2-yl)pent-4-enenitrile ***(1.84)***

This compound was prepared according to the general procedure using naphthoyl cyanide (0.18 g, 1.0 mmol) and 0.5 mL toluene to afford to product as an oil (0.216 g, 97%). **er** = 95:5. $\mathbf{[\alpha]_D}$ = -1.4° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 1.7 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.90 – 7.85 (overlap, 2H), 7.64 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.57 – 7.53 (overlap, 2H), 5.90 (dddd, *J* = 16.9, 10.2, 8.2, 6.4 Hz, 1H), 5.36 (dddd, *J* = 10.2, 1.2, 1.1, 1.0 Hz, 1H), 5.32 (dddd, *J* = 16.9, 1.3, 1.2, 1.2 Hz, 1H), 3.12 (s, OH),

2.91 (dddd, *J* = 13.9, 6.4, 1.3, 1.2 Hz, 1H), 2.82 (dddd, *J* = 14.0, 8.2, 1.2, 1.0 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 136.34, 133.55, 132.94, 130.41, 129.17, 128.56, 127.84, 127.15, 127.01, 124.65, 122.73, 122.27, 120.47, 73.62, 48.20. **ESI$^-$-MS** *m/z* calc'd for $[C_{15}H_{13}NO\text{-}H]^-$ 222.10, found 221.97.

(S)-2-hydroxy-2-(4-bromophenyl)pent-4-enenitrile ***(1.85)***

This compound was prepared according to the general procedure using 4-bromobenzoyl cyanide (0.21 g, 1.0 mmol) to afford to product as an oil (0.229 g, 91%). **er** = 98:2. **$[\alpha]_D$** = -2.7° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 5.87 (dddd, *J* = 17.1, 10.2, 8.3, 6.3 Hz, 1H), 5.38 (dddd, *J* = 10.2, 1.6, 0.9, 0.9 Hz, 1H), 5.31 (dddd, *J* = 17.1, 1.5, 1.5, 1.2 Hz, 1H), 2.96 (s, OH), 2.80 (dddd, *J* = 14.0, 6.3, 1.5, 0.9 Hz, 1H), 2.67 (dddd, *J* = 14.0, 8.3, 1.2, 0.9 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 138.22, 132.10, 129.98, 126.82, 123.49, 123.10, 120.02, 72.81, 48.31. **ESI$^-$-MS** *m/z* calc'd for $[C_{11}H_{10}BrNO\text{-}H]^-$ 249.99, found.

(S)-2-hydroxy-2-(4-chlorophenyl)pent-4-enenitrile ***(1.86)***

This compound was prepared according to the general procedure using 4-chlorobenzoyl cyanide (0.16 g, 1.0 mmol) to afford to product as an oil (0.171 g, 82%). **er** = 97:3. **$[\alpha]_D$** = -2.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 5.86 (dddd, *J* = 16.9, 10.2, 8.3, 6.4 Hz, 1H), 5.38 (dddd, *J* = 10.2, 1.6, 1.0, 0.9 Hz, 1H), 5.30 (dddd, *J* = 16.9, 1.6, 1.3, 1.2 Hz, 1H), 3.03 (s, 1H), 2.80 (dddd, *J* = 13.9, 6.4, 1.3, 1.0 Hz, 1H), 2.67 (dddd, *J* = 13.9, 8.3, 1.2, 0.9 Hz, 1H). **^{13}C**

NMR (125 MHz, Chloroform-*d*) δ 137.69, 135.33, 130.01, 129.13, 126.54, 123.05, 120.09, 48.35. **ESI$^-$-MS** *m/z* calc'd for $[C_{11}H_{10}ClNO\text{-}H]^-$ 206.05, found 206.03

(S)-2-hydroxy-2-(4-fluorophenyl)pent-4-enenitrile ***(1.87)***

This compound was prepared according to the general procedure using 4-fluorobenzoyl cyanide (0.15 g, 1.0 mmol) to afford to product as an oil (0.131 g, 69%). **er** = 96:4. $\mathbf{[\alpha]_D}$ = +0.6° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 8.8, 5.1 Hz, 2H), 7.11 (dd, *J* = 8.8, 8.7 Hz, 2H), 5.85 (dddd, *J* = 16.9, 10.2, 8.2, 6.5 Hz, 1H), 5.35 (dddd, *J* = 10.2, 1.6, 0.9, 0.9 Hz, 1H), 5.29 (dddd, *J* = 16.9, 1.6, 1.5, 1.2 Hz, 1H), 3.25 (s, OH), 2.79 (dddd, *J* = 14.0, 6.5, 1.5, 0.9 Hz, 1H), 2.69 (dddd, *J* = 14.0, 8.2, 1.2, 0.9 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 164.08, 162.10, 131.26, 131.18, 130.15, 127.08, 127.02, 122.83, 120.28, 115.98, 115.81, 72.81, 48.42. **ESI$^-$-MS** *m/z* calc'd for $[C_{11}H_{10}FNO\text{-}H]^-$ 190.07, found 190.04.

(S)-2-hydroxy-2-(3-fluorophenyl)pent-4-enenitrile ***(1.88)***

This compound was prepared according to the general procedure using 3-fluorobenzoyl cyanide (0.15 g, 1.0 mmol) to afford to product as an oil (0.133 g, 70%). **er** = 93:7. $\mathbf{[\alpha]_D}$ = +3.4° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.40 (m, 1H), 7.36 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.30 (ddd, *J* = 9.7, 2.3, 1.8 Hz, 1H), 7.09 (dddd, *J* = 8.2, 8.2, 2.6, 1.2 Hz, 1H), 5.88 (dddd, *J* = 17.0, 10.2, 8.3, 6.3 Hz, 1H), 5.39 (dddd, *J* = 10.2, 1.6, 0.9, 0.9 Hz, 1H), 5.32 (dddd, *J* = 17.0, 1.6, 1.5, 1.2 Hz, 1H), 3.03 (s, OH), 2.82 (dddd, *J* =

13.9, 6.3, 1.5, 0.9 Hz, 1H), 2.68 (dddd, *J* = 14.0, 8.3, 1.2, 0.9 Hz, 1H). **ESI⁻-MS** *m/z* calc'd for $[C_{11}H_{10}FNO\text{-}H]^-$ 190.07, found.

(S)-2-hydroxy-2-(4-nitrophenyl)pent-4-enenitrile ***(1.89)***

This compound was prepared according to the general procedure using 4-nitrobenzoyl cyanide (0.18 g, 1.0 mmol) and 0.5 mL toluene to afford to product as an oil (0.152 g, 70%). **er =** 96:4. $\mathbf{[\alpha]_D}$ = (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 5.88 (dddd, *J* = 16.9, 10.2, 8.4, 6.4 Hz, 1H), 5.42 (dddd, *J* = 10.2, 1.5, 1.0, 0.9 Hz, 1H), 5.32 (dddd, *J* = 16.9, 1.5, 1.3, 1.1 Hz, 1H), 3.37 (s, 1H), 2.85 (dddd, *J* = 13.9, 6.4, 1.3, 1.0 Hz, 1H), 2.68 (dddd, *J* = 14.0, 8.4, 1.1, 0.9 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 145.75, 129.57, 129.39, 126.37, 124.19, 123.94, 119.58, 72.51, 48.49. **ESI⁻-MS** *m/z* calc'd for $[C_{11}H_{10}N_2O_3\text{-}H]^-$ 217.07, found.

(S)-2-hydroxy-2-(4-trifluoromethylphenyl)pent-4-enenitrile ***(1.90)***

This compound was prepared according to the general procedure using 4-trifluoromethylbenzoyl cyanide (0.20 g, 1.0 mmol) to afford to product as an oil (0.194 g, 80%). **er =** 97:3. $\mathbf{[\alpha]_D}$ = (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.74 – 7.69 (overlap, 4H), 5.88 (dddd, *J* = 16.9, 10.1, 8.4, 6.3 Hz, 1H), 5.40 (dddd, *J* = 10.1, 1.4, 1.1, 0.9 Hz, 1H), 5.32 (dddd, *J* = 16.9, 1.4, 1.3, 1.2 Hz, 1H), 3.18 (s, OH), 2.84 (dddd, *J* = 13.9, 6.3, 1.3, 1.1 Hz, 1H), 2.69 (dddd, *J* = 14.0, 8.3, 1.2, 0.9 Hz, 1H).

(R)-2-(furan-2-yl)-2-hydroxypent-4-enenitrile ***(1.91)***

This compound was prepared according to the general procedure using 2-furoyl cyanide (0.12 g, 1.0 mmol) to afford to product as an oil (0.057 g, 35%). **er** = 85:15. **$[\alpha]_D$** = (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.47 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.56 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.41 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.86 (dddd, *J* = 16.3, 10.9, 7.7, 6.9 Hz, 1H), 5.36 (m, 1H), 5.33 (m, 1H), 3.05 (s, OH), 2.95 (dddd, *J* = 14.0, 6.9, 1.2, 1.2 Hz, 1H), 2.90 (dddd, *J* = 14.0, 7.7, 1.1, 1.1 Hz, 1H).

(±)-2-hydroxy-2-(thiophen-2-yl)pent-4-enenitrile ***(1.92)***

This compound was prepared according to the general procedure using 2-thiophenecarbonyl cyanide (0.24 g, 1.0 mmol) to afford to product as an oil (0.141 g, 50%). **er** = 50:50. **$[\alpha]_D$** = 0.0 (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.28 (dd, *J* = 3.6, 1.3 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.89 (dddd, *J* = 17.0, 10.2, 7.7, 6.8 Hz, 1H), 5.38 – 5.32 (overlap, 2H), 3.23 (s, OH), 2.94 – 2.85 (overlap, 2H).

General Procedure for the Preparation of Chiral Homoallylic Cyanohydrins

To an oven dried reaction tube charged with a stir bar was added (*R*)-Ph_2BINOL (0.057 g, 0.15 mmol), *tert*-butanol (0.19 mL, 2.0 mmol), and *B*-*E*-crotyl-1,3,2-dioxaborinane (0.21 g, 1.5 mmol). The tube was purged with argon, and the reaction allowed to stir at room temperature for 30 minutes. To the reaction was then added benzoyl cyanide (0.131 g, 1.0 mmol) and it was allowed to stir for 16 hours at room temperature. The crude reaction mixture was dry loaded onto silica and purified *via* flash chromatography,

elution with DCM. The product was isolated as a pale yellow oil (0.180 g, 96% yield). **er** = 92:8. **dr** = 178:1. **$[\alpha]_D$** = +48° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.45 – 7.37 (overlap, 3H), 5.94 (ddd, *J* = 17.0, 10.3, 8.6 Hz, 1H), 5.39 (ddd, *J* = 10.3, 1.6, 0.7 Hz, 1H), 5.36 (ddd, *J* = 17.0, 1.6, 0.9 Hz, 1H), 3.19 (s, OH), 2.64 (dddd, *J* = 8.6, 6.9, 0.9, 0.7 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 137.87, 137.19, 129.38, 128.77, 125.98, 120.88, 119.40, 77.44, 50.78, 15.47. **ESI$^-$-MS** *m/z* calc'd for $[C_{12}H_{13}NO\text{-}H]^-$ 187.10, found 187.04.

(2S,3R)-2-hydroxy-3-methyl-2-phenylpent-4-enenitrile ***(1.105)***

This compound was prepared according to the general procedure using *B-Z*-crotyl-1,3,2-dioxaborinane (0.21 g, 1.5 mmol) to afford the product as a pale yellow oil (0.159 g, 85%). **er** = 88:12. **dr** = 8:1. **$[\alpha]_D$** = +8.1° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.43 – 7.37 (overlap, 3H), 5.76 (ddd, *J* = 17.2, 10.5, 7.3 Hz, 1H), 5.18 (ddd, *J* = 10.5, 1.2, 1.2 Hz, 1H), 5.10 (ddd, *J* = 17.2, 1.3, 1.3 Hz, 1H), 2.93 (s, OH), 2.81 (dddd, *J* = 7.3, 6.8, 1.3, 1.2 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 138.44, 136.31, 129.23, 128.68, 125.77, 120.27, 119.10, 77.14, 48.67, 13.74. **ESI$^-$-MS** *m/z* calc'd for $[C_{12}H_{13}NO\text{-}H]^-$ 187.10, found 187.0.

CHAPTER TWO. Asymmetric Petasis Reaction with Glycolaldehyde

Introduction

Beta-amino alcohols are abundant in natural products and pharmaceuticals and can be found in compounds such as those used for the treatment of asthma[31], epilepsy[32], central nervous system diseases[33], and cancer[34]. One challenging aspect of accessing these compounds, and many other enantioenriched compounds, is the installation of the chiral center. Means of generating the stereocenter include starting with commercially available chiral material, using a chiral auxiliary, separation by chiral resolution, or asymmetric catalysis. In the case of G Protein-Coupled Receptor 88 (GPR88) modulators, the original synthesis started with a commercially available, chiral aryl amino ester (**2.1**, Figure 2.1). After seven linear steps, four of which are protections and deprotections, the desired product **2.8** was obtained.

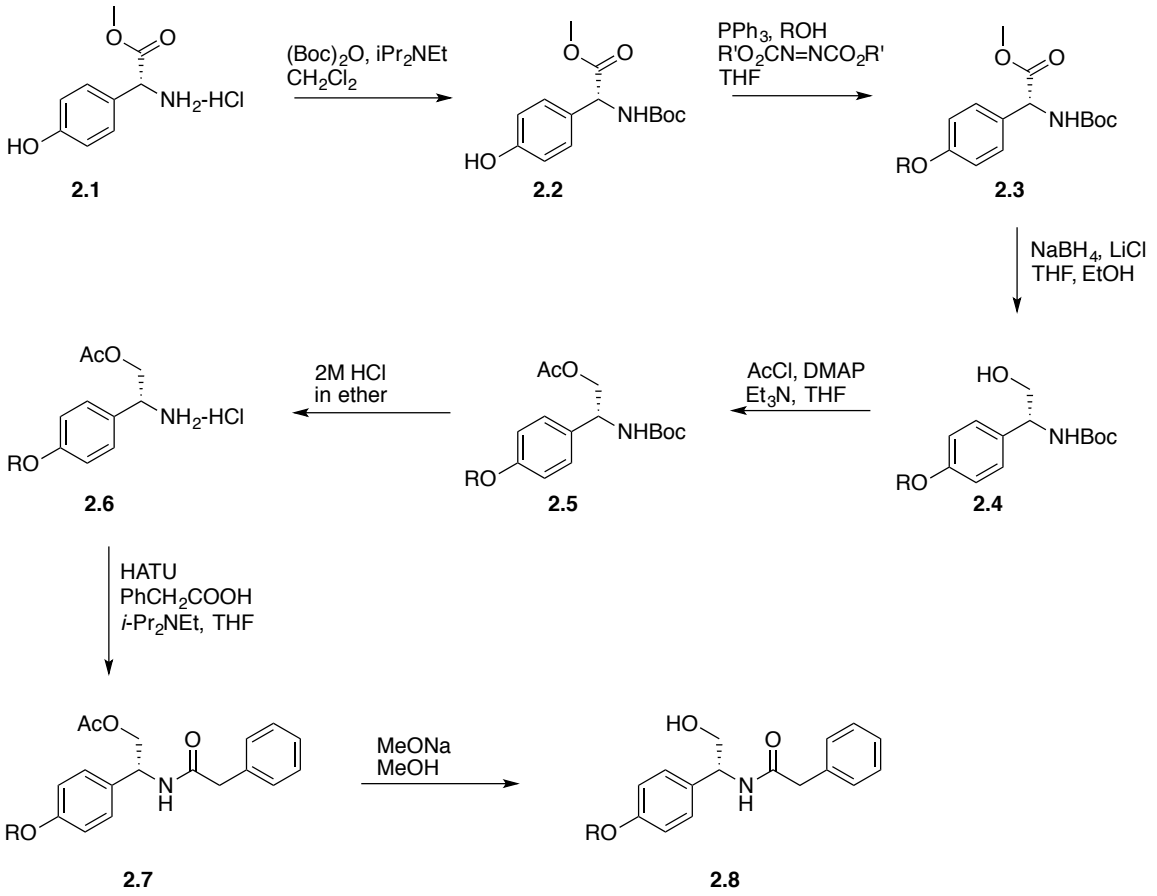


Figure 2.1. Patent synthesis of GPR88 Modulator

An alternative to starting with commercially available material is utilizing a chiral auxiliary to set the desired stereocenter in a diastereoselective fashion, and then removing the auxiliary to afford the final product. An example of this strategy is the Ellman chiral sulfinyl imine.[35] In this work, Ellman and co-workers used a diastereoselective Grignard reaction to access the β-amino alcohol. In two straightforward steps, they were able to generate protected β-amino alcohol **2.12** with good yield and selectivity (Figure 2.2). Condensation between sulfinamide **2.09** and benzyloxy aldehyde **2.10** furnished the electrophilic imine in 97% yield (**2.11**). Subsequent addition of a phenyl Grignard

reagent gave the protected amino alcohol in 98:2 dr. Following hydrolysis of the amine and cleavage of the benzyl group, the aryl glycinol would be obtained.

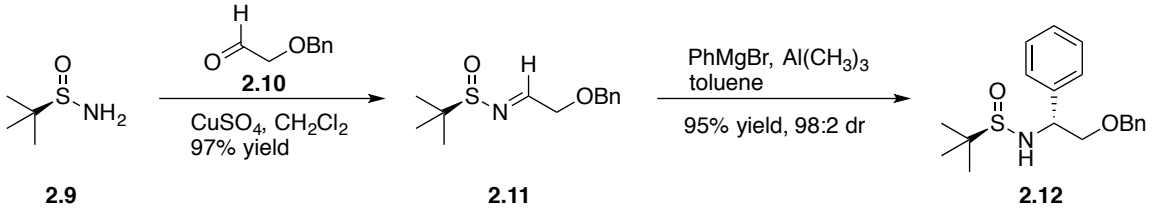
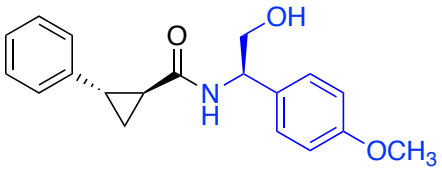


Figure 2.2. Sulfinamide chiral auxiliary for β-amino alcohols

An example of the chiral sulfinamide procedure is in the synthesis of Lu AF58801, a potent α7 nicotinic acetylcholine receptor modulator and potential schizophrenia treatment (Figure 2.3)[36]. The highlighted β-amino alcohol component of the compound was accessed using Ellman's method in 85% overall yield. Subsequent hydrolysis of the sulfinyl group, deprotection of the alcohol, and coupling to a carboxylic acid yielded the desired amido alcohol.



Lu AF58801

Figure 2.3. Alpha-7 nicotinic acetylcholine receptor modulator

A route to enantiopure β-amino alcohols through the use of chromatographic separation was reported by Umani-Ronchi in 2001[37] (Figure 2.4). In this work, the authors performed a dihydroxylation on styrene **2.13**, followed by a Ritter rearrangement to produce racemic amino alcohol **2.15**. At this stage in the synthesis, Umani-Ronchi incorporated a chiral acyl chloride to give a diastereomeric mixture of amide **2.17**.

Hydrolysis of the acetate, separation of diastereomers, and successive amide cleavage provided desired amino alcohol **2.19**.

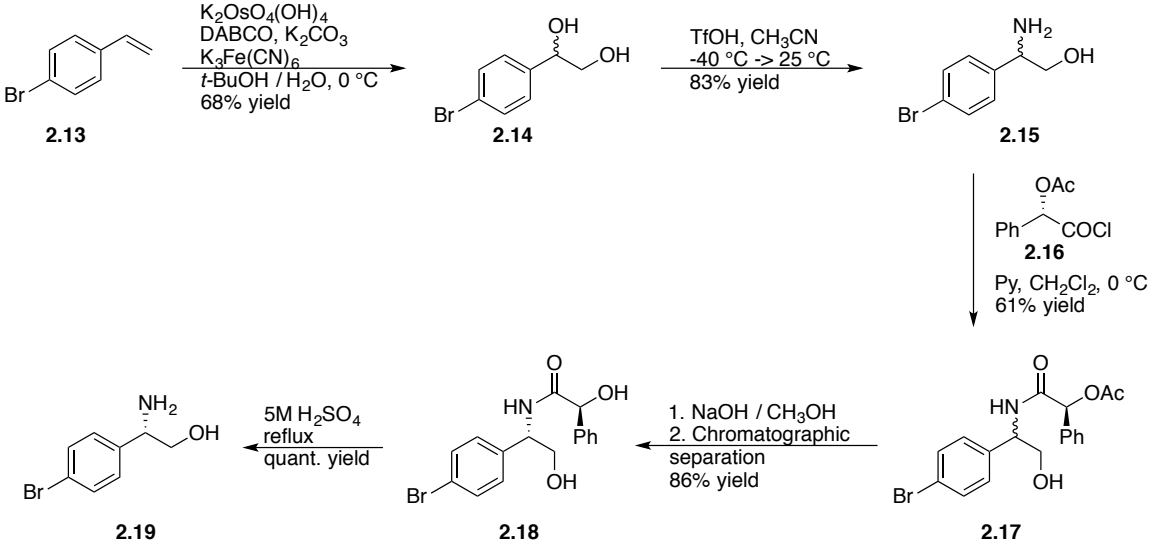


Figure 2.4. Chromatographic separation of diastereomers

While all of these routes effectively access β-amino alcohols, they require careful selection of reagents to not alter the preinstalled stereocenter, manipulation of functional groups, or use chiral auxiliaries and disposal of half of the material after chromatographic separation. These drawbacks can be addressed by implementing a direct enantioselective, direct synthesis. An example of such a catalytic asymmetric process is the osmium-catalyzed aminohydroxylation of styrenes reported by K. Barry Sharpless[38] (Figure 2.5). In the presence of osmium, $(DHQ)_2PHAL$, and benzyl carbamate **2.21**, *p*-benzyloxystyrene was converted to the corresponding amino alcohols in 76% yield, 98.5:1.5 er, and an 88:12 ratio of regioisomers **2.22** and **2.23**. Sharpless and co-workers also noted that the regioselectivity could be controlled through solvent and catalyst choice.

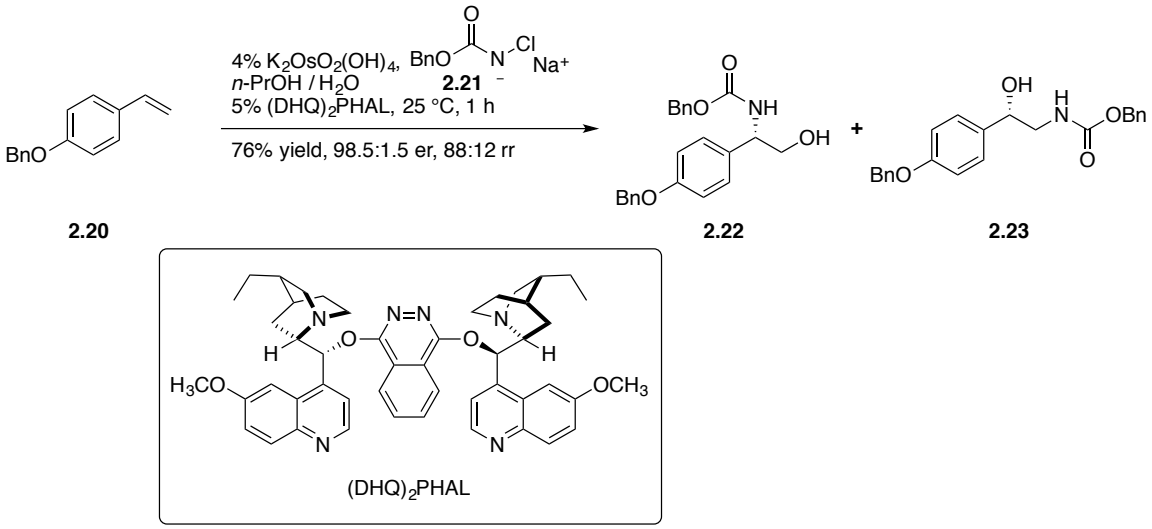


Figure 2.5. Sharpless asymmetric aminohydroxylation

Multiple applications of this methodology have been shown in the syntheses of biologically active compounds. Dale Boger's first and second generation syntheses of Teicoplanin, an antibiotic similar to Vancomycin, utilized the asymmetric aminohydroxylation to generate the amino alcohols used to install the F and G rings of the macrocycle (Figure 2.6)[39,40]. The asymmetric aminohydroxylation was also implemented in the synthesis of a phenylglycinol GPR88 receptor agonist patented by BMS and Lexicon Pharmaceuticals[33,41].

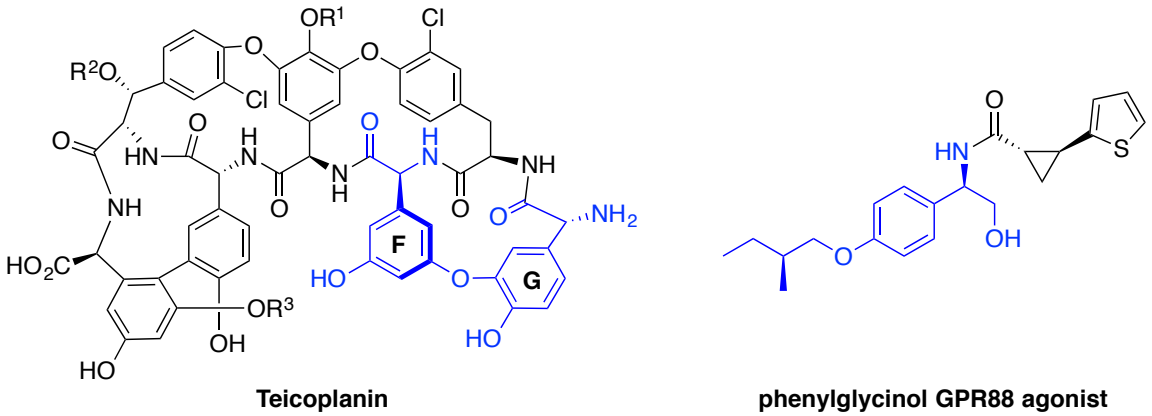


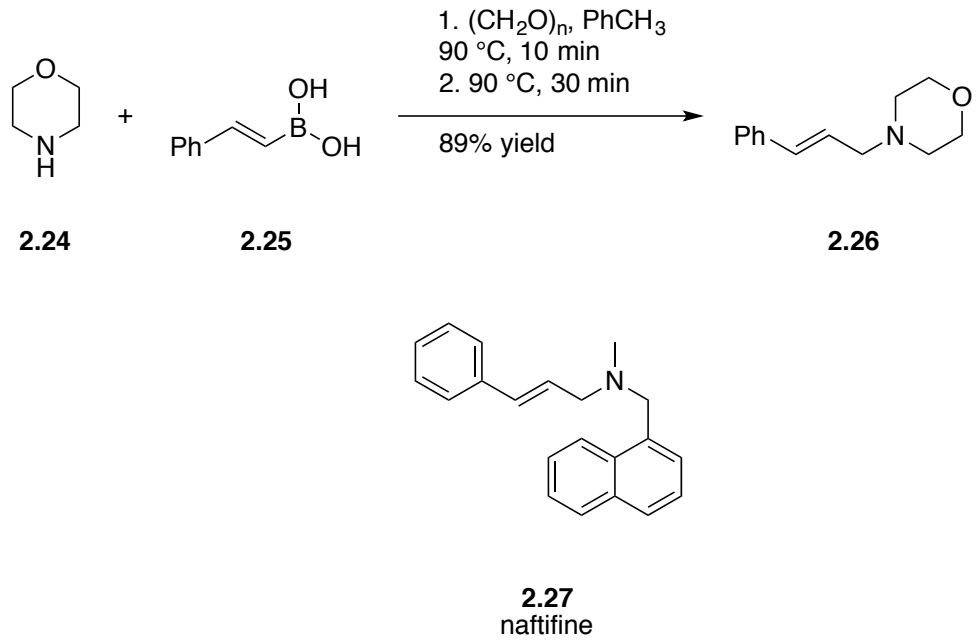
Figure 2.6. Teicoplanin and phenylglycinol GPR88 receptor agonist

While an improvement compared to the other routes, the regioselectivity of the aminohydroxylation is very substrate dependent. Styrene **2.20** performed second only to *p*-phenylstyrene (91:9), with most other substrates giving 75:25 regiomeric ratio or lower. Three cases – styrene, *p*-acetoxystyrene, and *p*-tosyloxystyrene – yielded little to no regiocontrol. The desire for an approach that is both enantio- and regioselective, as well as step and atom economical led us to explore the Petasis reaction as a means for accessing amino alcohol compounds.

Background

The Petasis Reaction

As demonstrated above, β-amino alcohols are important synthetic targets. Such structures can be accessed through the Petasis reaction, a multicomponent reaction (MCR) also referred to as the boronic acid Mannich reaction. This reaction was discovered in 1993 by Petasis and Akritopoulou[42] and offers an efficient route for syntheses of β-amino alcohols, α-amino acids, α-aryl glycines, and other chemical skeletons.[43] It involves the combination of a primary or secondary amine, a boronic acid, and an aldehyde. The first Petasis reaction was between secondary amines, paraformaldehyde, and alkenyl boronic acids (Figure 2.7). With morpholine, **2.24**, as the amino component and styrenyl boronic acid **2.25**, the allylic amine product **2.26** was obtained in 89% yield as a single diastereomer. This new methodology was applied to the synthesis of antifungal agent naftifine[44].



2.24 **2.25** **2.26**

2.27
naftifine

Figure 2.7. First example of the Petasis reaction

The study of MCRs has become more prominent in recent years due to their simplicity and atom economy.[45–47] Surprisingly, there are very few examples of catalytic enantioselective Petasis reactions to date.[48–53] Our interest in this project arises from the robust nature of the Petasis reaction as well as the lack of publications on the asymmetric process.

Previous Catalytic Asymmetric Methods

Takemoto's group reported the first catalytic asymmetric Petasis-type reaction in 2007[52] (Figure 2.8). Through a multicomponent approach, the quinoline could act as an

imine surrogate. After *in situ* formation of a carbamate with **2.29**, the quinoline

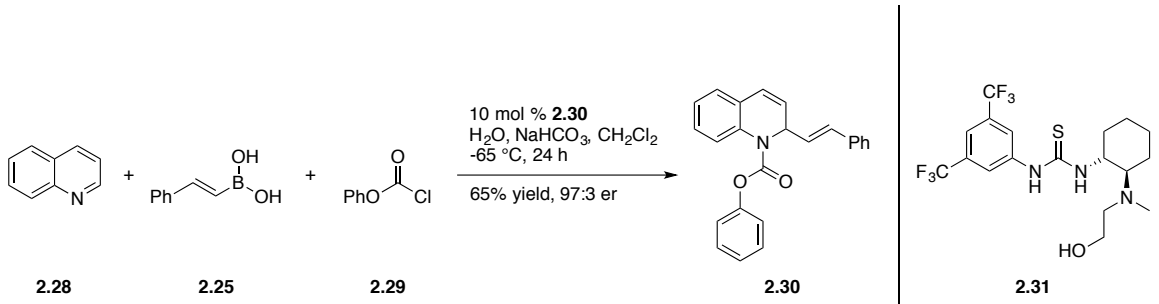


Figure 2.8. Petasis-type reaction of quinolines

would become more electrophilic and therefore susceptible to nucleophilic addition from the boronic acid. Their bifunctional thiourea catalyst **2.31** would simultaneously activate **2.25** to the ate complex while H-bonding to the electrophile. This produced their product in 65% yield and 97:3 er. By varying the quinolone substitution at C3 and C6, and the aryl substituents on the boronic acid, they synthesized 10 additional substrates with yields ranging from 28% – 78%, and selectivities of 91:9 – 98.5:1.5.

An enantioselective Petasis reaction was later reported by the Schaus group, and focused on the development of an method to access enantioenriched α-amino esters.[53] Using styrenyl diethyl boronate **2.32**, dibenzylamine **2.33**, and ethyl glyoxylate **2.34** in the presence of a vaulted biaryl diol catalyst, (*S*)-VAPOL[54] at -15 °C, they were able to access α-amino ester product **2.35** in 81% yield and 95.5:4.5 er (Figure 2.9). This work represents the first formal catalytic enantioselective Petasis methodology. We determined our method to be amenable to a selection of styrenyl and alkenyl boronates as well as ten other secondary amines. Coupling products were obtained in yields up to

94% and er's up to 98.5:1.5. Aromatic boronates, however, did not participate well as reaction partners.

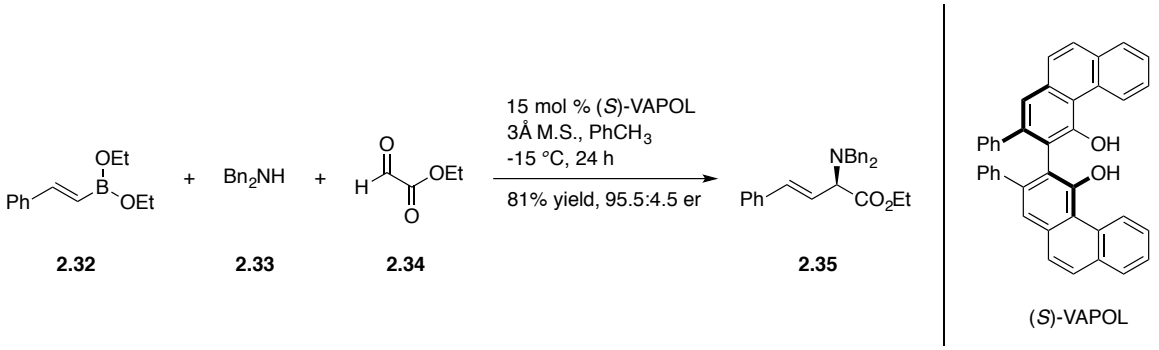


Figure 2.9. Enantioselective Petasis synthesis of α-amino esters

Takemoto also reported a thiourea-catalyzed enantioselective Petasis methodology for the synthesis of α-amino amides in 2011.[50] Using 2-oxoacetamide **2.36** with aniline **2.37** and diisopropyl styrenyl boronate **2.38** in the presence of hydroxy-thiourea catalyst **2.40** gave desired product **2.39** in 74% yield and 96:4 er (Figure 2.10). Their substrate scope shows yields ranging from 54% – 86% and selectivities from 90:10 – 96.5:3.5 er. The reaction tolerated other electron-rich anilines with extended reaction times of 48 and 72 hours when paired with the unsubstituted styrenyl boronate. Electron rich, electron deficient, and heteroaromatic styrenyl boronates were also amenable to the reaction conditions. Takemoto demonstrated the reaction's scope by examining peptides as the amino component. He was able to generate di- and tripeptides by altering the N-substitution on the 2-oxoacetamide coupling partner in moderate yields and moderate to good enantio- and diastereoselectivities.

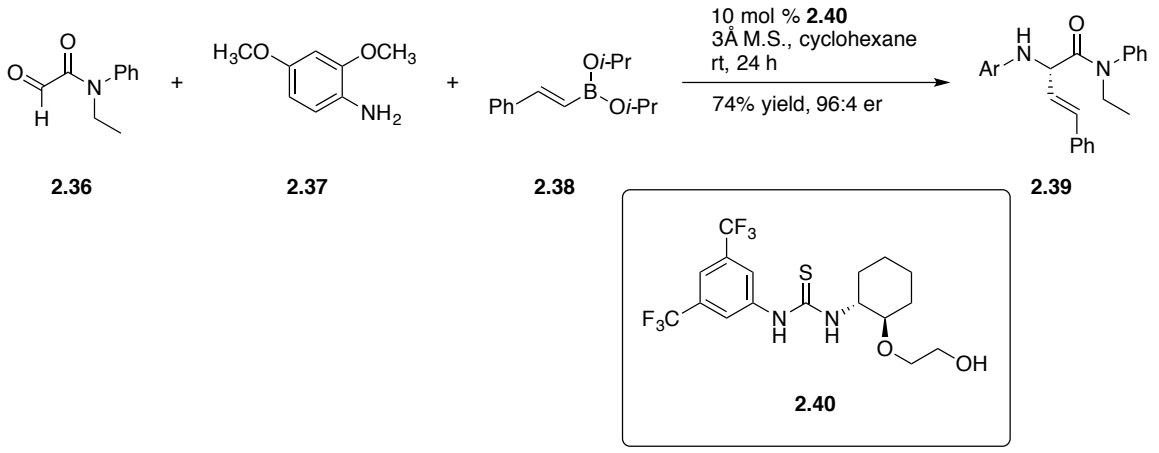


Figure 2.10. Asymmetric synthesis of α-amino amides

Wei-Cheng Yuan's group reported the first enantioselective Petasis reaction of salicylaldehyde in 2012[48] (Figure 2.11). With thiourea-BINOL **2.45** as their catalyst, they proposed an exchange between the aromatic boronic acid and BINOL OH groups, in

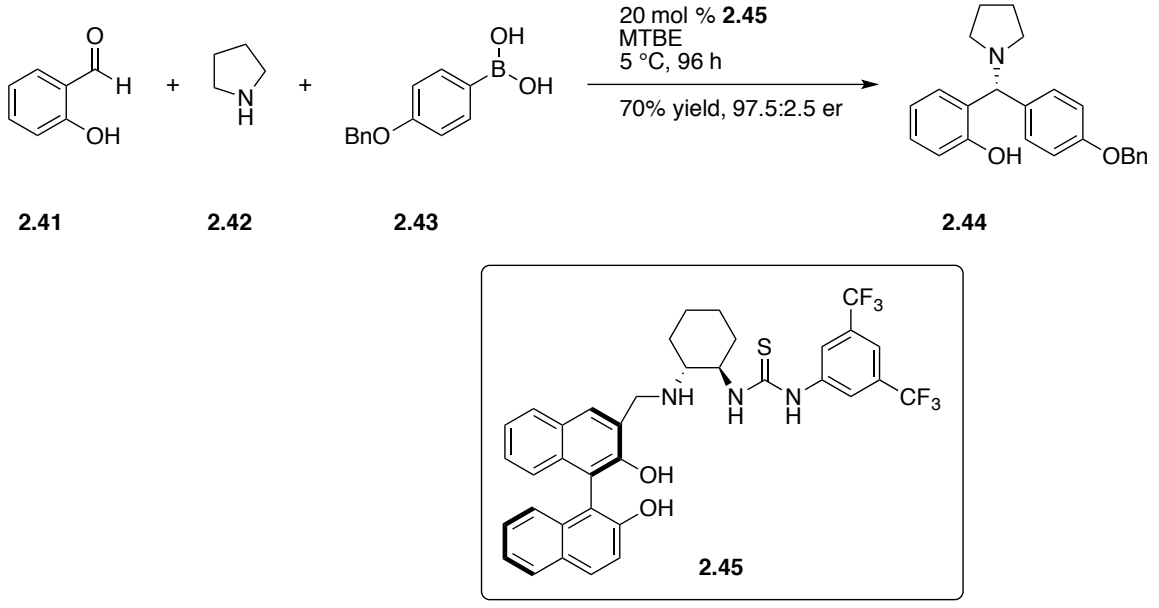


Figure 2.11. Thiourea-BINOL catalyzed Petasis reaction of salicylaldehyde

addition to salicylaldehyde imine coordination by hydrogen bonding to the thiourea functionality. This complexation would provide the chiral environment necessary to

produce the desired amino phenol product **2.44** in 70% yield and 97.5:2.5 er. In contrast to our work, Yuan proposed a double exchange between boronic acid **2.43** and the catalyst. As a control experiment to probe this hypothesis, they looked at substituting one of the BINOL OH groups with an OPiv, and isolated 60% of **2.44** with a greatly compromised selectivity of 52.5:47.5 er.

The Yuan group later reported that the thiourea substitution on BINOL was not essential to their selectivity[49]. Conducting the same reaction in mesitylene at 0 °C for 93 hours gave a comparable yield of **2.44** in 83.5:16.5 er (Figure 2.12, Eq. 1). They also demonstrated that styrenyl boronic acids could participate in the transformation. Styrenyl boronic acid **2.25** and morpholine **2.24** reacted with salicylaldehyde in 24 hours to give amino phenol **2.47** in 84% yield and 93:7 er (Figure 2.12, Eq. 2). Through the same

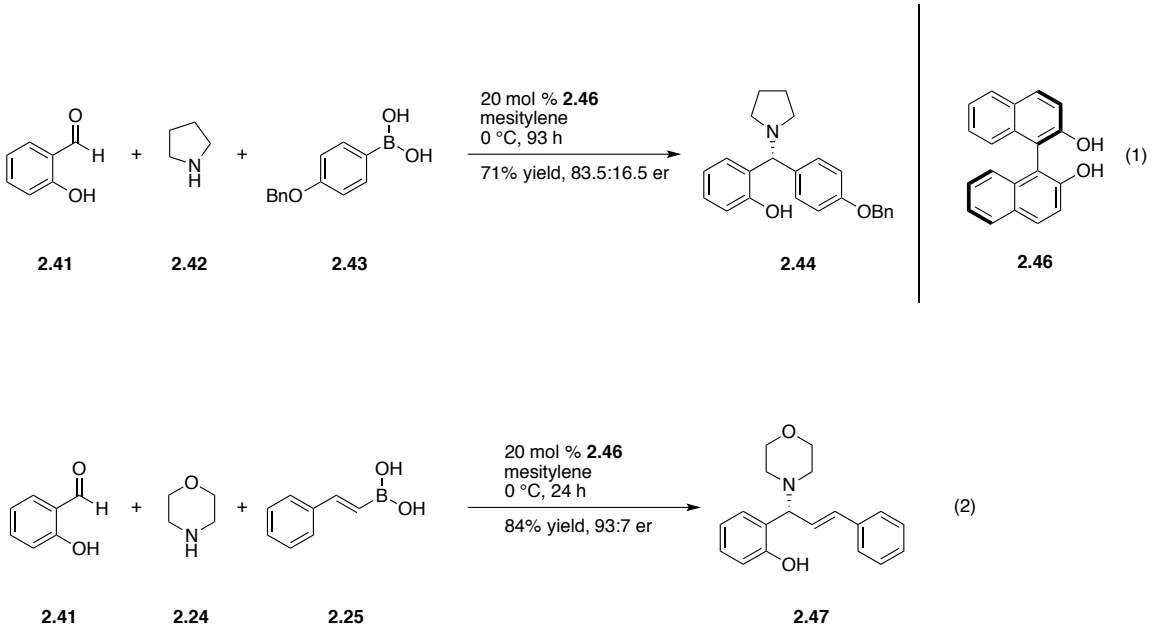


Figure 2.12. BINOL catalyzed Petasis reaction of salicylaldehyde

double exchange between the boronic acid and BINOL, Yuan proposed the salicylaldehyde phenol oxygen would directly coordinate with boron's empty *p*-orbital to generate the ate complex and allow for nucleophilic delivery of the boronic acid functionality to the iminium intermediate.

Xin and co-workers reported a BINOL-catalyzed enantioselective Petasis reaction with vinyl boronates in 2013[51]. Vinyl dibutyl boronate **2.49** reacted with salicylaldehyde and piperidine **2.48** in the presence of 20 mol % 3,3'-dimethylBINOL **2.51** to give aminophenol **2.50** in 92% yield and 99.25:0.75 er (Figure 2.13). Impressively, this yield

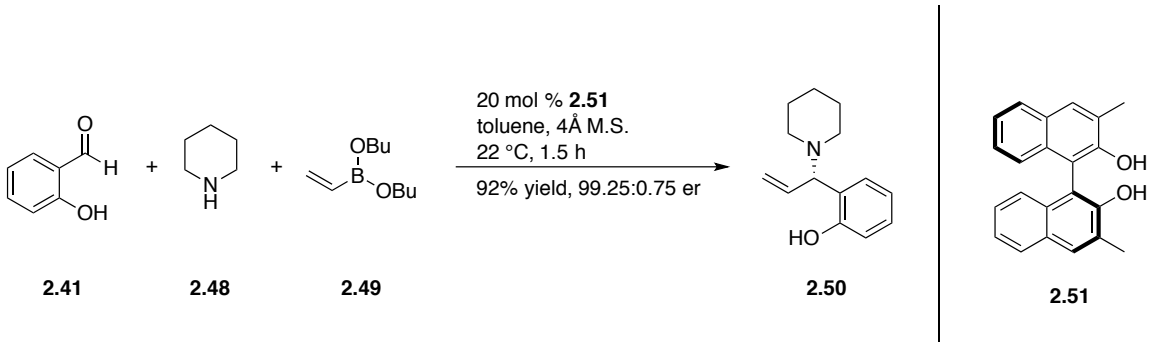


Figure 2.13. Room temperature Petasis reaction of salicylaldehyde

and selectivity were achieved at room temperature after 1.5 hours. This is in direct contrast to previous methodologies that proceed for 1 day or more, under cooling. They then probed the BINOL-boronate exchange mechanism by ^{1}H and ^{11}B NMR studies. Examining the boronate with 1 equivalent of BINOL and molecular sieves in CD_2Cl_2 showed no change in the aromatic region of the proton NMR and no new signal in the boron NMR, indicating no new complexes were being formed. The addition of 1 equivalent of diethylamine resulted in the appearance of new peaks in both the proton and

boron NMRs. Based on this information, Xin proposed a mechanism in which the amine promotes the exchange between boronate and catalyst.

Examples of catalytic enantioselective Petasis reactions are emerging in the literature, but there remains a gap in methods to make chiral β-amino alcohols. While enantioselective routes have not yet been reported, diastereoselective methods have been seen. An examination of these methods will be discussed in the following section.

Diastereoselective Petasis Synthesis of β-Amino Alcohols

Work in this area conducted by Petasis and Zavialov demonstrated the possibility of performing the Petasis reaction diastereoselectively in the synthesis of β-amino alcohols[55]. They showed that *anti*-1,2-amino alcohols can be accessed in 70% yield with >99.5:0.5 dr and er, starting from an enantioenriched α,β-dihydroxyaldehyde (Figure 2.14). Beginning with enantiopure glyceraldehyde **2.53**, a single diastereomer and enantiomer was obtained from the Petasis reaction after deprotections of the benzhydril amine and conversion to its corresponding Boc-amine. Petasis also examined other α-substituted hydroxyaldehydes as well as glycolaldehyde dimer in his synthesis of β-amino alcohols. In the case of glycolaldehyde dimer, racemic products were obtained.

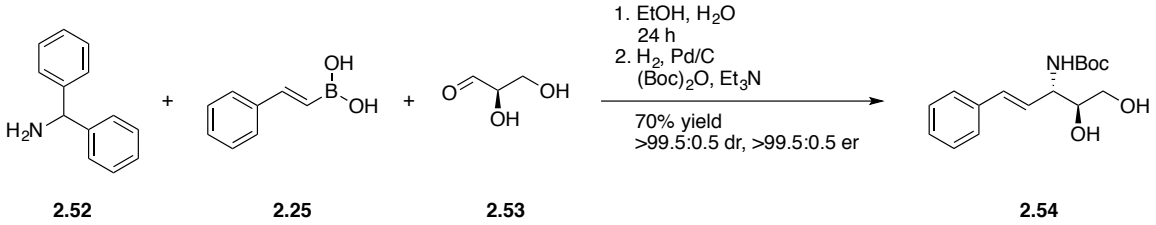


Figure 2.14. Diastereoselective Petasis reaction of glyceraldehyde

The Schaus group also reported the development of a diastereoselective Petasis reaction[56]. With the use of glycolaldehyde dimer, both *anti*- and *syn*-selective products were obtained through the use of enantioenriched chiral diol catalysts (Figure 2.15). Reacting phenylglycine methyl ester **2.55** with glycolaldehyde dimer **2.56** and diethyl styrenylboronate **2.32** in the presence of molecular sieves and 3,3'-dibromoBINOL gave the desired amino alcohol product. It was discovered that by switching between the (*R*) and (*S*) catalysts, we could tune the reaction to proceed with either *anti*- or *syn*-selectivity, respectively. Running a control reaction with no catalyst showed that the transformation had a natural bias of 4:1 *syn* diastereomeric ratio with 81% isolated

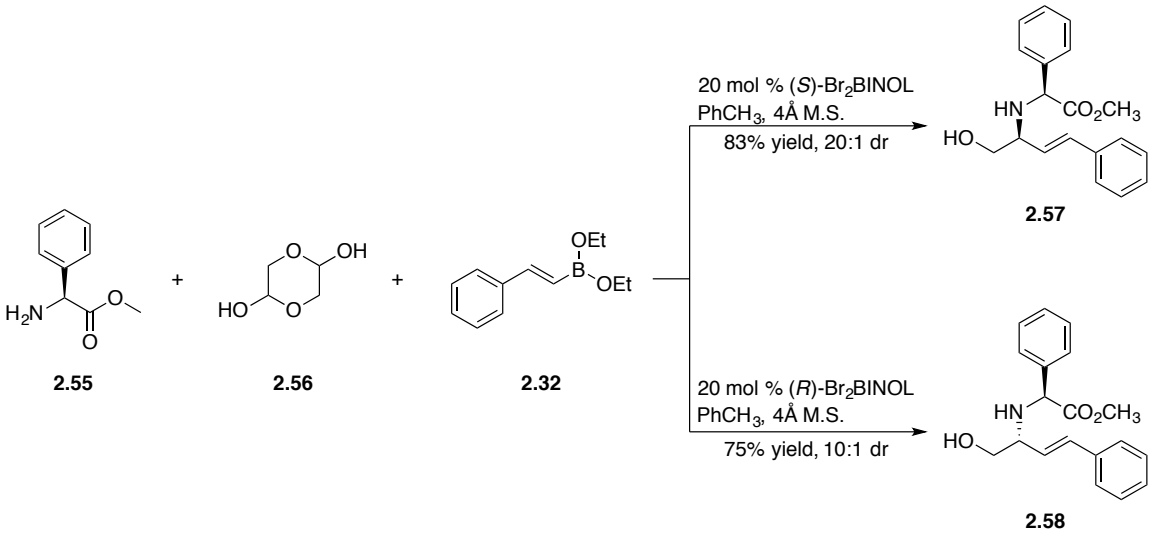


Figure 2.15. *Syn*- and *anti*-selective Petasis reaction of glycolaldehyde dimer

yield of product **2.57**. Using the (*S*) enantiomer of our catalyst enhanced the dr to 20:1 while maintaining the yield of the reaction. In contrast, employing the (*R*) enantiomer of the catalyst reversed the selectivity to 10:1 of the *anti*-product, **2.58**, in 75% yield. With these results in hand, we began investigations toward the application of this methodology

to glycolaldehyde and its derivatives for the enantioselective synthesis of β-amino alcohols.

Results and Discussion

Enantioselective Synthesis of β-Amino Alcohols

To initiate studies on the enantioselective pathway, the reaction of commercially available glycolaldehyde dimer **2.56**, 1,1-di(*p*-anisyl)methylamine (DAM amine) **2.59**, and 4-methoxyphenylboronic acid diethyl ester **2.60** was carried out at room temperature in toluene with 4 mol % (*R*)-3,3'-Br_2BINOL in the presence of 3Å molecular sieves resulting in >80% yield and >98:2 er of desired amino alcohol product **2.61** (Figure 2.16).

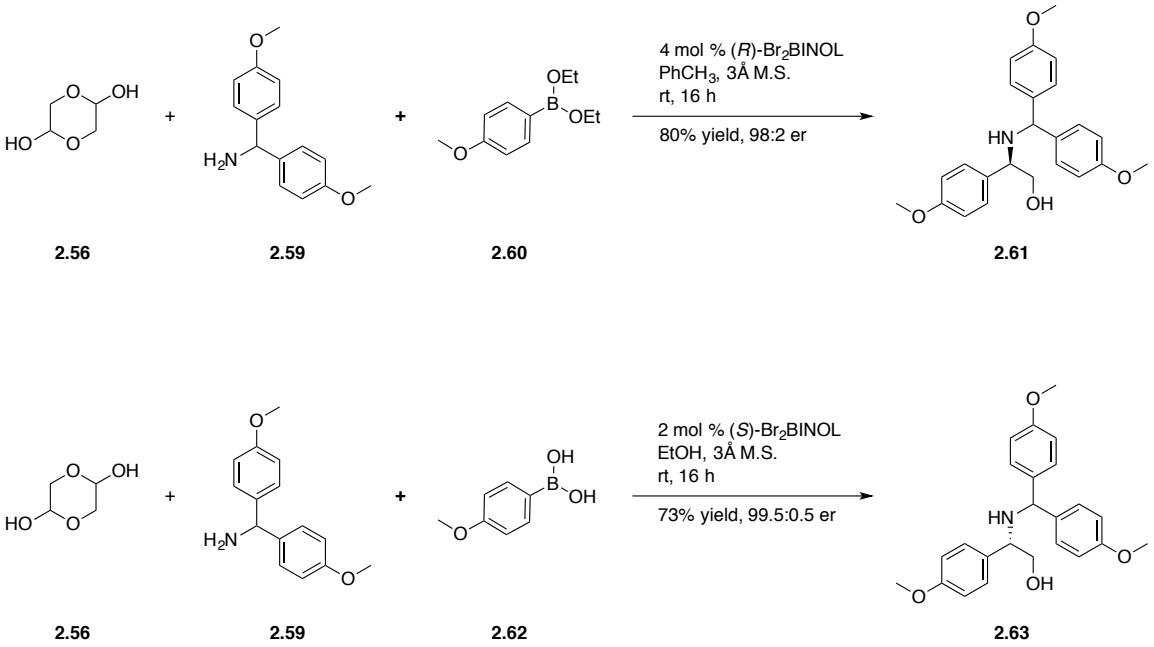


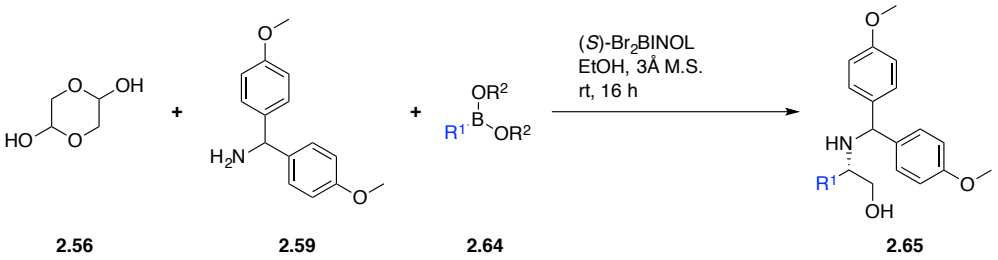
Figure 2.16. Optimization of the enantioselective Petasis reaction of glycolaldehyde

Although an exciting result, further optimization of reaction conditions was done to eliminate the necessity of preparing the air- and moisture-sensitive boronate ester. Based on the procedure for obtaining the diethyl boronate, we proposed an *in situ* formation of boronate from the corresponding boronic acid would occur when using ethanol as the solvent in place of toluene, in the presence of molecular sieves as a desiccant.

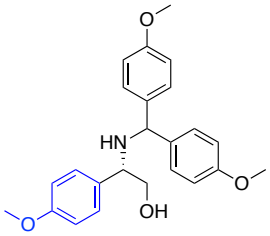
The aforementioned procedural modification proved to be fruitful in the application of this methodology to boronic acids. For the parent reaction with 4-methoxyphenylboronic acid **2.62**, the yield dropped slightly to 73%, but an enhancement in the enantioselectivity of product **2.63** to nearly a single enantiomer was observed even with a decrease in catalyst loading from 4 mol % to 2 mol %.

Boronic Acid Substrate Scope

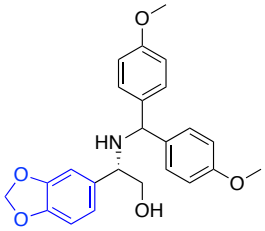
After optimization of the parent reaction, the conditions were successfully applied to the boronic acids shown in Figure 2.17. A few exceptions were encountered in the process of expanding the substrate scope. Products **2.70**, **2.72**, and **2.74** showed good yields, but the rate of exchange of the corresponding boronic acids with the catalyst was too slow to substantially affect the enantioselectivities. For these cases, we prepared the diethyl boronate derivatives and found an increase in selectivities accompanied by a slight decrease in yields of the resulting products. Products **2.66** – **2.69** and **2.73** were obtained using 4 mol % (*S*)-3,3'-Br_2BINOL, while all others used 8 mol % catalyst.



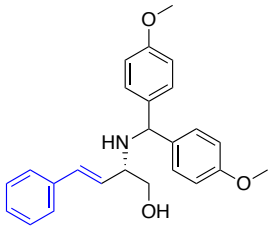
2.56 **2.59** **2.64** **2.65**



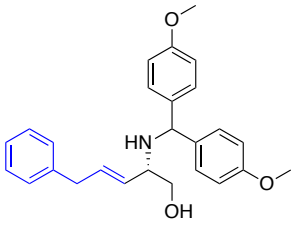
2.63, 73% yield, 99.5:0.5 er



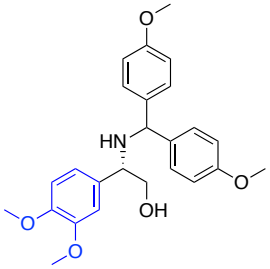
2.66, 71% yield, 98:2 er



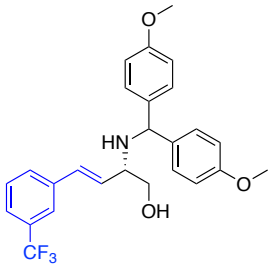
2.67, 78% yield, 98:2 er



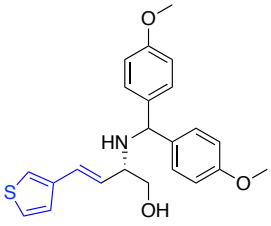
2.68, 84% yield, 99.5:0.5 er



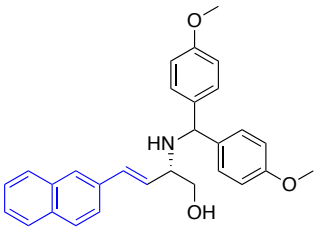
2.69, 83% yield, 96:4 er



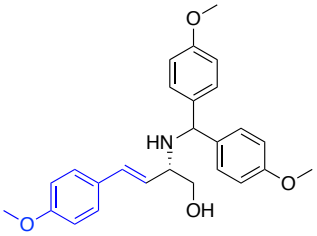
2.70, 62% yield, 98:2 er
R^2 = Et



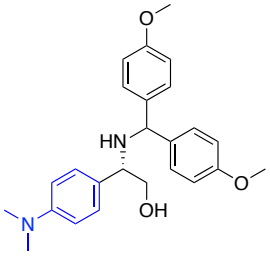
2.71, 74% yield, 95:5 er



2.72, 88% yield, 98.5:1.5 er
R^2 = Et



2.73, 88% yield, 93:7 er



2.74, 89% yield, 99.5:0.5 er
R^2 = Et

Figure 2.17. Boronic acid substrate scope: Enantioselective synthesis of β-amino alcohols

Amine Substrate Scope

Once the reaction had been shown to accommodate structurally diverse boronates, we shifted our attention to varying the amine component. Choosing the parent boronic acid **2.62**, along with two others based on their results with DAM amine, we began to screen primary and secondary amines in a combinatorial fashion. We found that electronically diverse primary aromatic amines all participated well in the reaction (Figure 2.18). Electron neutral aniline provided product **2.78** in 71% yield and 90:10 er, and product **2.81** in 75% yield and 94:6 er. Electron rich anisidine afforded amino alcohols **2.79**, **2.82**, and **2.83**. The compounds were isolated in yields from 73% - 92%, and selectivities from 94:6 – 97:3 er. Finally, electron deficient 2-bromoaniline produced desired product **2.80** with a selectivity of 99:1 and an isolated yield of 70%.

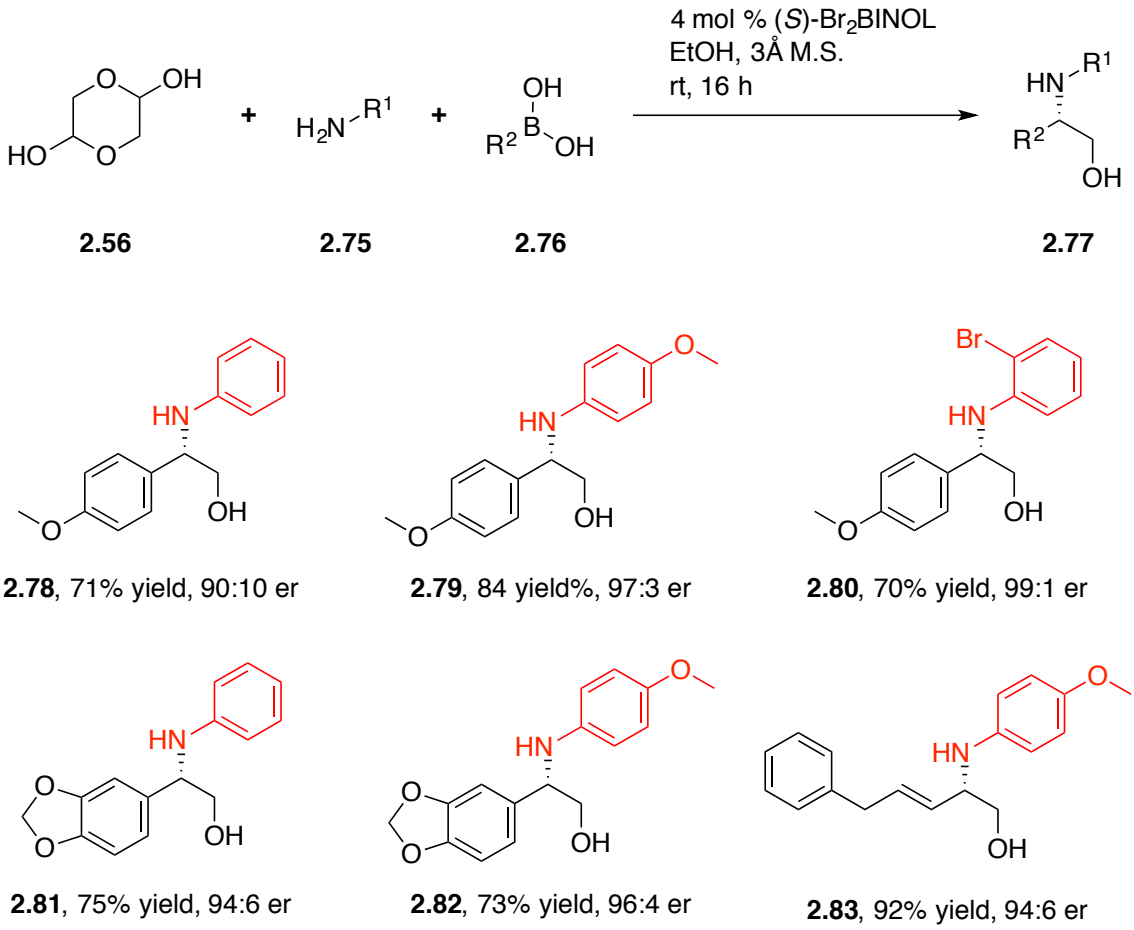


Figure 2.18. Primary amine substrate scope

Both cyclic and acyclic secondary amines also participated in the reaction (Figure 2.19). Morpholine afforded both products **2.87** and **2.92** in roughly 80% yield with good enantioselectivities. Dibenzylamine proved to be a good reaction partner with 4-methoxyphenylboronic acid and 3,4-(methylenedioxy)phenylboronic acid to give compounds **2.88** and **2.90**, but displayed compromised enantioselectivity when reacting with 3-phenyl-1-propen-1ylboronic acid, producing **2.93** in 90% yield and 82:18 er. Lastly, N-methylaniline reacted to give products **2.89** and **2.91** both in 67% yield with 87:13 and 91:9 er, respectively. Notably, reactions with secondary amines required

increased catalyst loading from 4 mol % to 8 mol %. This can be attributed to the faster reaction with the iminium intermediate formed with the secondary amines when compared to the imine formed with the primary amines. While the reaction demonstrated tolerability to multiple amino reaction partners, very electron-poor amines, such as carbamates, led to complete recovery of starting materials.

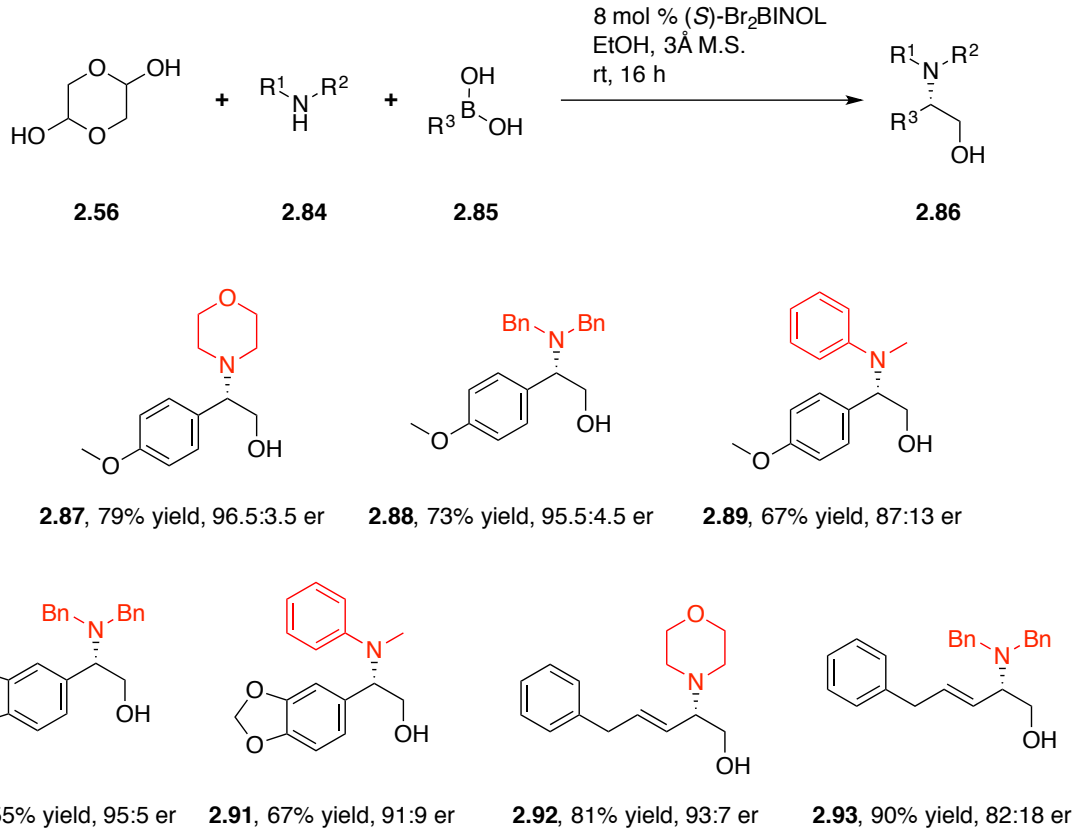


Figure 2.19. Secondary amine substrate scope

Proposed Mechanism

With a complete understanding of reaction scope, we proposed a catalytic cycle accounting for the observed selectivity (Figure 2.20). Boronic acid **2.85** first undergoes

single exchange with ethanol to give boronate **2.95**. In agreement with our previously proposed mechanisms[15,18], boronate **2.95** exchanges once again, this time with biphenol catalyst **2.94**. At this point, hemiaminal **2.97**, formed *in situ* between amine **2.84** and aldehyde **2.56**, coordinates with the empty *p*-orbital on the boron in complex **2.96** to give the boron-ate complex. Intermediate **2.98** then undergoes boronic acid assisted dehydration, yielding new cyclic intermediate **2.99**. The proximity of the reactive hemiaminal and boron-ate complex moieties facilitates transfer of the aryl group from the boron to the hemiaminal carbon, giving way to desired product **2.86** and regenerating the catalyst for entry into another cycle.

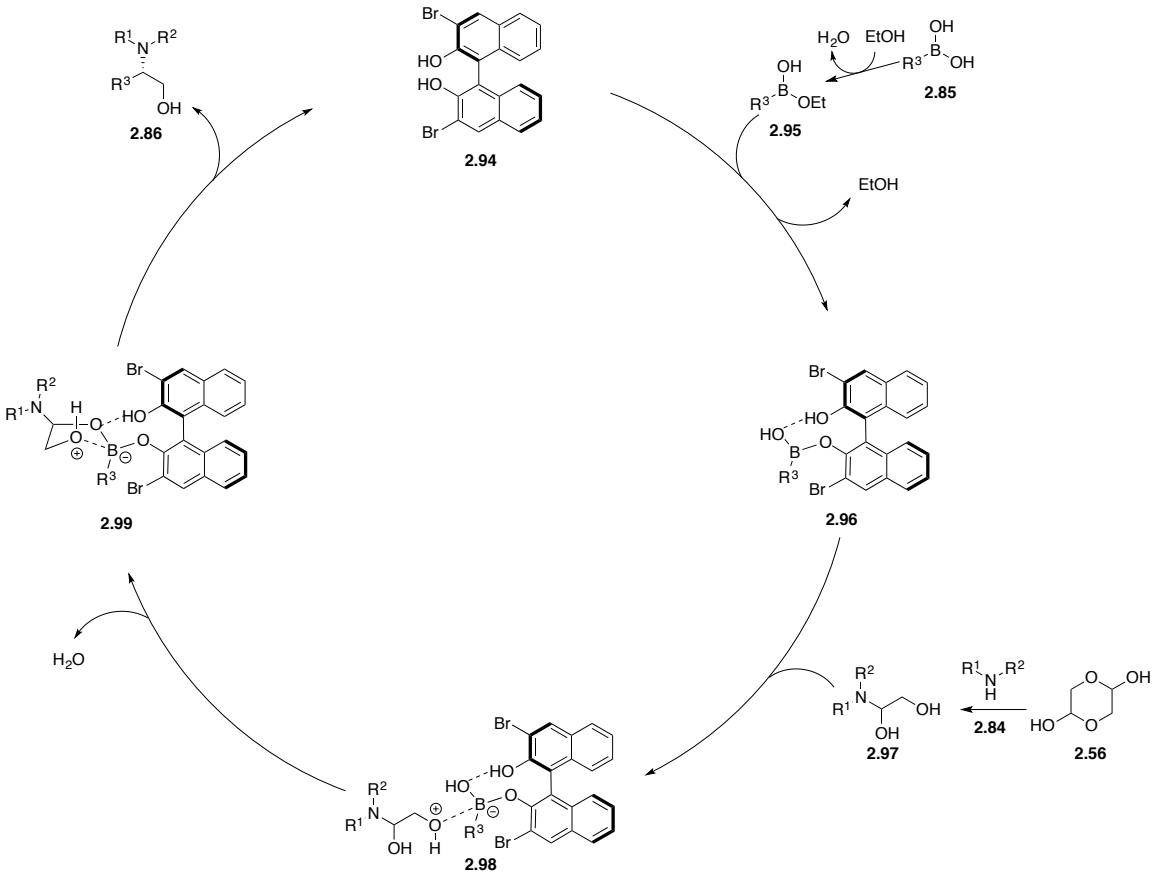


Figure 2.20. Proposed catalytic cycle

In order to elucidate this mechanism, we performed mass spectrometry studies on a reaction mixture 2 hours into reaction time. Initially, it was found that the DAM group is extremely labile in the mass spectrometer, making it difficult to interpret the data, so morpholine was chosen as the model amine for future experiments. Using negative mode electron spray direct inject MS, masses corresponding to reaction intermediates were observed (Figure 2.21). The region from 625 – 750 m/z is magnified 4 times compared to the rest of the spectrum, and a base peak is seen at 442.9 m/z. This corresponds to the deprotonated (*S*)-Br_2BINOL **2.100**. The peaks at 578.3, 646.8, 707.2, and 737.1 m/z can

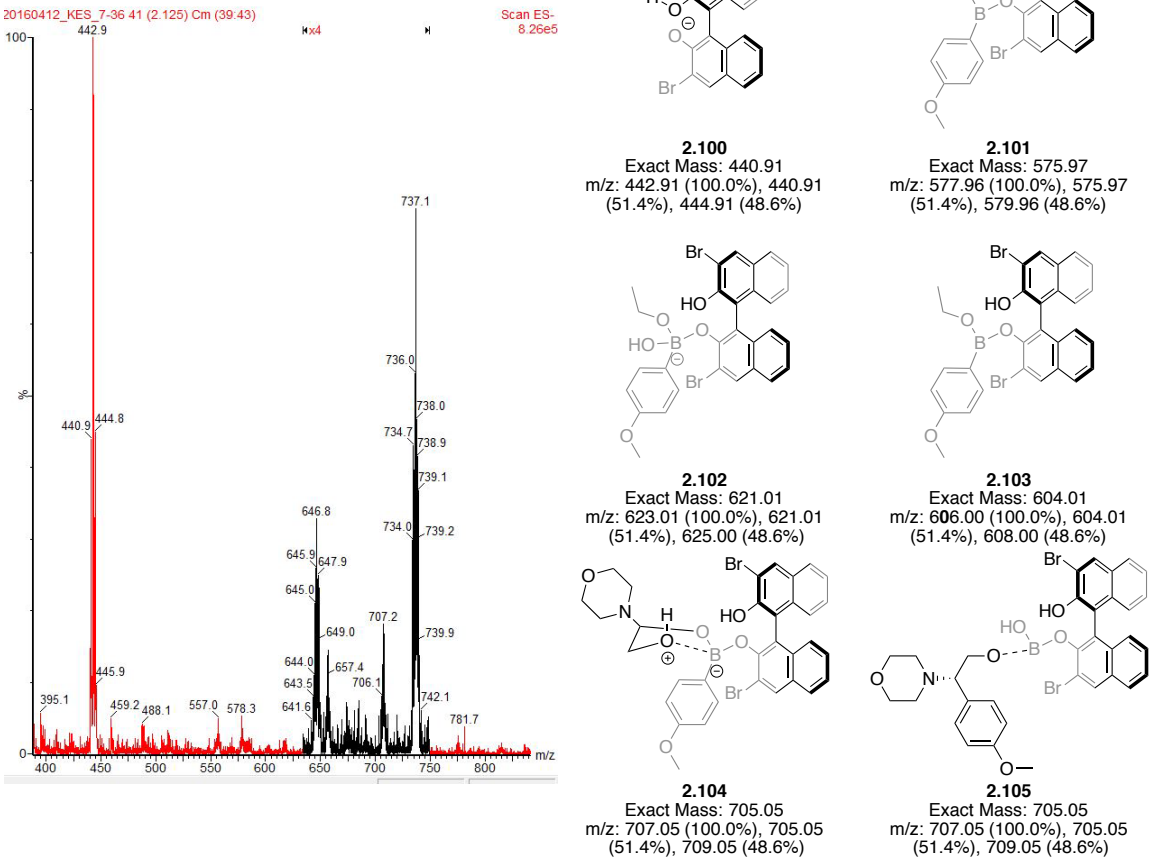
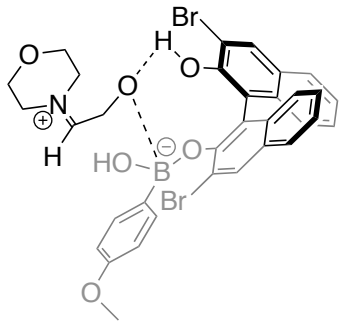


Figure 2.21. ESI$^-$ mass spectrometry experiment

all be attributed to catalyst complexes expected to form over the course of the reaction. A compound formed from single exchange between the catalyst and boronic acid, **2.101**, would be seen at 578 m/z. The peak at 646.8 m/z could either be the M+Na adduct of **2.102** (646 m/z) or the M+CH_3CN adduct of **2.103** (647 m/z). We expect the complex formed from coordination of a cyclic hemiaminal to boron's empty *p*-orbital in the chiral boronate species, as shown in **2.104**, to produce the peak at 707.2 m/z. The peak at 707.2 could also be attributed to product bound to the catalyst immediately after transfer of the aryl group from the boron-ate, as indicated in **2.105**. Finally, the peak at 737 m/z can be accounted for as the trifluoroacetic acid [M+114] adduct of **2.102**[57,58].

These observations not only corroborate our proposed mechanism, but also lend insight to the asymmetric induction observed. In stereoselectivity model **2.106**, the boronate-catalyst complex positions the boronate and its components in the back plane, leaving the front plane available for coordination of the iminium (Figure 2.22). This facially selective coordination is assisted by a hydrogen bond between the catalyst and the β-hydroxy group on the hemiaminal. This geometry allows for the boronate substituent to be delivered to the *si*-face of the iminium, giving rise to the (*S*)-product.

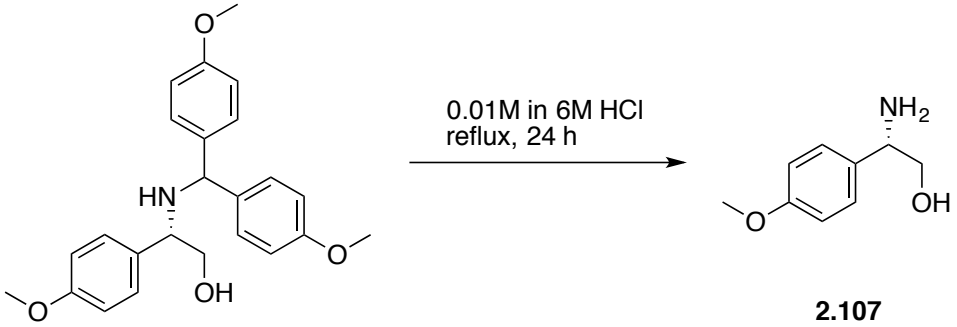


2.106

Figure 2.22. Stereoselectivity model for the Petasis reaction of glycolaldehyde

Assignment of Absolute Stereochemistry

In an effort to confirm the proposed chiral intermediate, we turned to determination of absolute stereochemistry. The free amine analogue of **2.63** is reported in the literature[59] and a simple acid deprotection of the DAM group would allow for the comparison of optical rotations (Figure 2.23). Refluxing the protected amino alcohol in HCl followed by basic work-up provided **2.107**. Comparison with the literature indicated free amine **2.107**, and therefore also compound **2.63**, exist as the (*S*)-enantiomer ($[\alpha]_{D,exp}$ = +26°, $[\alpha]_{D,lit}$ = +22.6°). This absolute stereochemistry is in agreement with our predicted enantioselectivity model, and helps to further support our proposed mechanism.



2.63 **2.107**

Figure 2.23. Deprotection of DAM β-amino alcohol

Scale-up and Catalyst Recycling Studies

We then set out to determine the scalability and catalyst recycling efficiency of our methodology. This would be examined using anisidine as the model substrate, due to

its cost economy compared to DAM amine. To begin, we wanted to optimize the molecular sieve loading for the reaction. At 500 mg 3Å M.S. per mmol of amine, we were concerned with how they could affect the stirring capacity of our reaction on larger scales. In comparison to the model reaction, we evaluated the loading at 200 mg/mmol and 100 mg/mmol (Figure 2.24). At the standard 500 mg, product *ent*-**2.79** was obtained

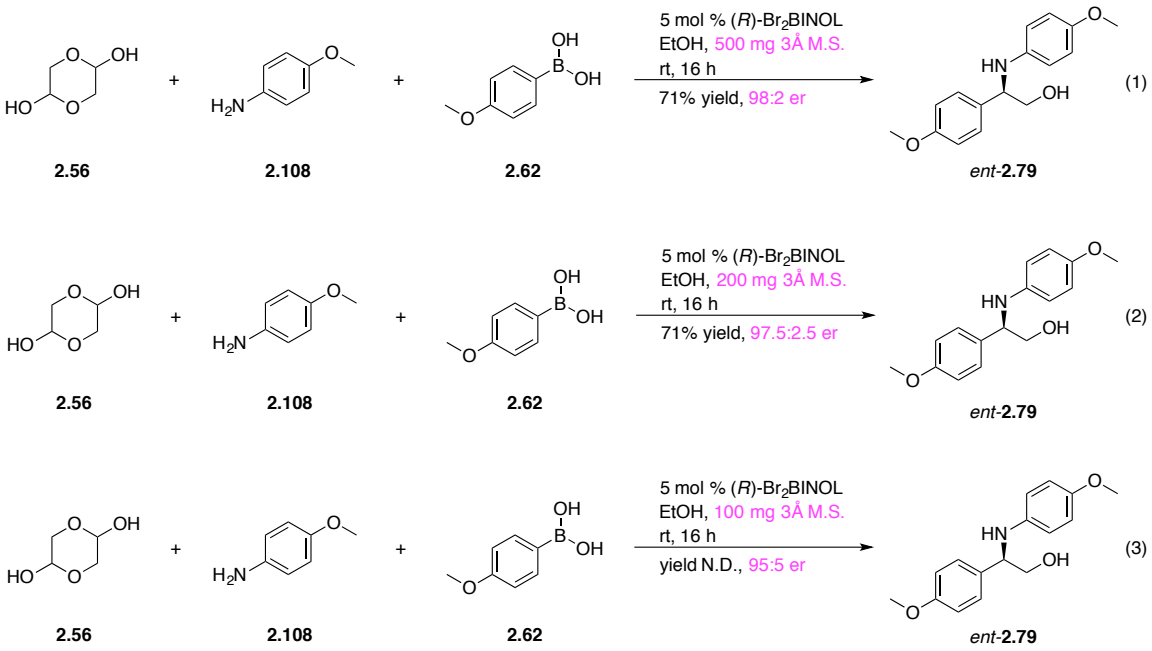


Figure 2.24. Molecular sieve loading study

in 71% yield and 98:2 er. Lowering the loading by 60% to 200 mg provided the product in comparable yield and selectivity. Dropping it further to 100 mg led to a drop in selectivity down to 95:5 er. This difference, while small, is enough to be a potential problem at larger scales, so the isolated yield was not determined, and 200 mg/mmol was chosen as the optimal ratio for scale-up trials.

To start scale-up studies, reactions were examined at the 4 mmol scale. This is a 4X enhancement of substrate **2.108** from the standard reaction, and would yield 1 gram of

product. Under the new molecular sieve loading conditions, product *ent*-**2.79** was obtained in 76% isolated yield and 97:3 er (Figure 2.25). With comparable results to the standard reaction scale, we proceeded to incrementally increase the scale of the reaction.

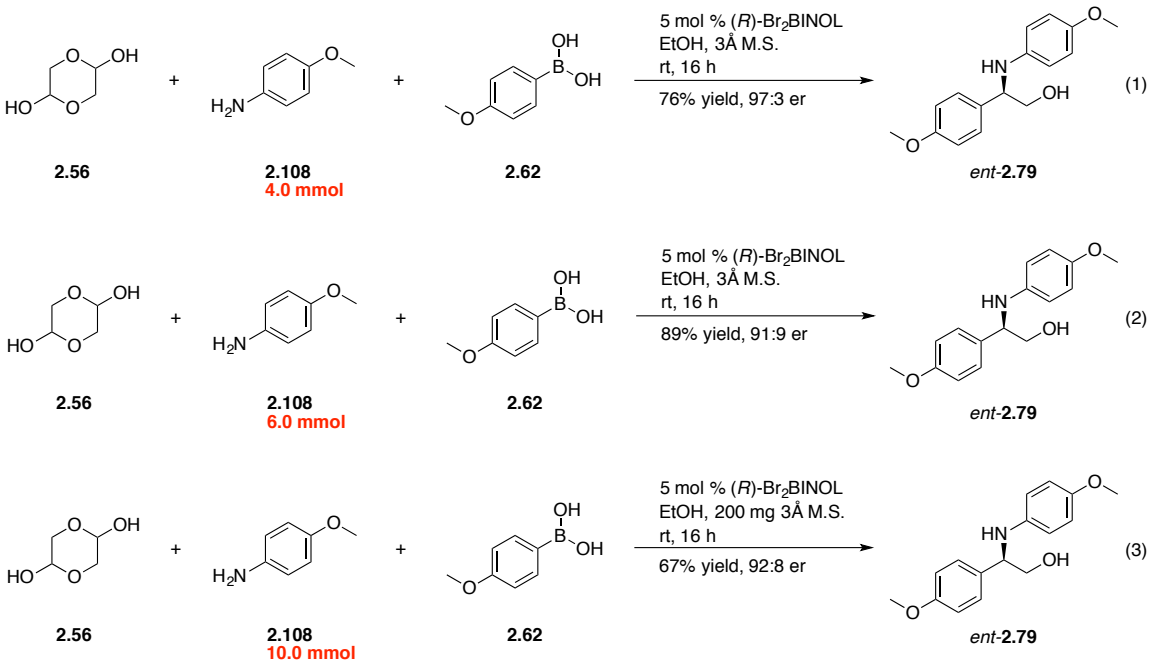


Figure 2.25. Preliminary scale-up studies

Unfortunately, when investigating the scalability at the 6 mmol and 10 mmol scales, we saw a retention of yield, but a significant drop in selectivity to 91:9 and 92:8 er, respectively. We propose this loss of selectivity has to do with the reaction vessel's ability to remove heat from the reaction. According to reports on scaling up reactions, the decrease in ratio of vessel surface area to reaction volume leads to a decreased ability to remove heat from the reaction[60,61]. This inability to efficiently remove heat would increase the overall temperature, and therefore the overall rate, of the reaction. This increase would enhance the racemic rate of the reaction and lend to decreased enantioselectivities. In an effort to combat this spontaneous exotherm, we ran the 4

mmol and 6 mmol scale reactions by submerging the reaction flask in a room temperature water bath, in hopes that it would facilitate pulling the excess heat out of the reaction (Figure 2.26). We observed a slight enhancement in selectivity on the 4 mmol scale to 98:2 er, with a retention of yield. On the 6 mmol scale, we saw a decrease in yield to 72% from 89%, accompanied by an increase in selectivity from 91:9 er to 96:4 er. The

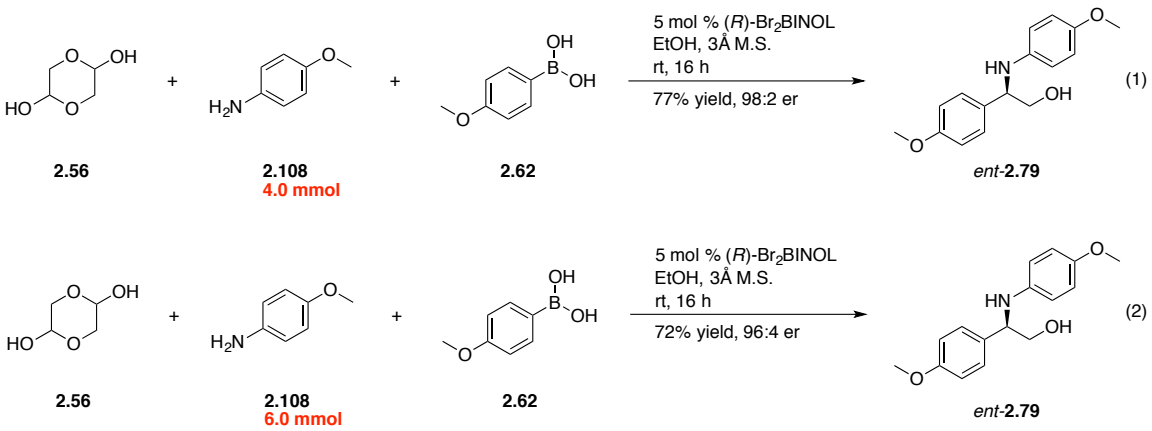


Figure 2.26. Room temperature water bath cooled scale-up reactions

drop in yield can be explained by a decreased overall reaction rate expected upon removal of heat from the reaction. While the enantiomeric ratio did increase, it is still below the benchmark selectivity for the standard reaction scale. Further investigations can be done to further remove heat from the reaction, such as running it in an ice bath, or in a jacketed reactor.

Upon scale-up of the reactions, we became interested in catalyst recyclability; at 5 mol % catalyst loading, the 6 mmol scale reaction requires 173 mg of catalyst. We used this reaction scale to evaluate the recoverability and recyclability of the Br_2BINOL

catalyst (Figure 2.27). After basic aqueous work-up to extract the product,

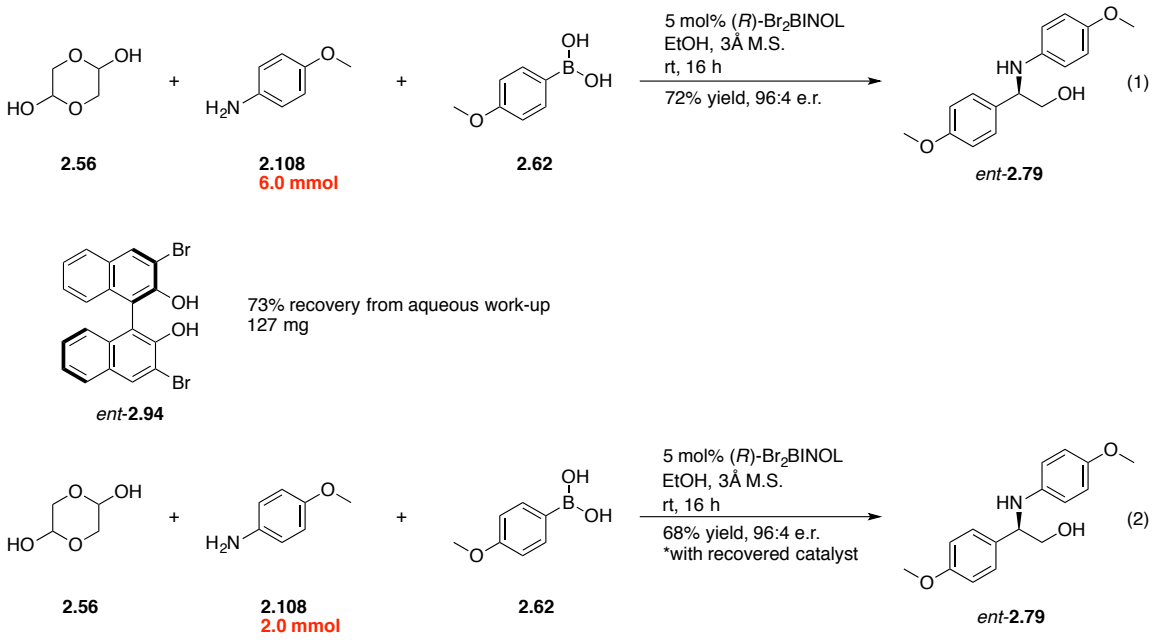


Figure 2.27. Recovery and recycling of catalyst

the basic phase was acidified and the extracted. From that, catalyst *ent*-**2.94** was recovered in 73% yield. This material was recrystallized and re-subjected to the reaction at a 2 mmol scale. The desired amino alcohol was isolated in 68% yield and 96:4 er, a complete retention of both yield and selectivity.

Conclusion

In conclusion, we have successfully developed the first asymmetric Petasis reaction for the synthesis of β-amino alcohols through the use of (S)-3,3'-Br_2BINOL as a catalyst. This methodology was applied to both aryl and vinyl boronic acids and boronates. Though this substrate scope experiences a limitation with electron-deficient aromatic boronates, studies to improve their participation in the reaction have been performed, and will be discussed in Chapter Three. We were also able to extend this reaction to include different primary and secondary amines, which go through both the imine and iminium intermediate, respectively. This difference in intermediates presents different rates of reactivity, but we are able to achieve high enantioselectivities in both cases.

Through the deprotection of compound **2.62**, we have determined the absolute stereochemistry of our products and used this information to propose a catalytic cycle that is supported by mass spectrometry data. Our enantioselectivity model based on a single exchange of the boronate with the catalysts accurately predicts the observed absolute stereochemistry. Through direct inject mass spectrometry, we identified intermediates to support this single exchange hypothesis. We observed masses corresponding to both boronic acid and boron-ate singly exchanged with the catalyst, as well as a mass relating to either iminium bound to the catalyst/boronate complex, or product bound to it. Although structural information is not available *via* mass spectrometry, we are confident in our mass-based structural assignments.

Finally, we were able to successfully scale up the reaction from a 250 mg scale to a 1.5 g scale. More specifically, through the use of a room temperature water bath we were able to disperse heat out of the reaction on larger scales and minimize the decrease in selectivity that could be caused by rate enhancement from the spontaneous exotherm. The catalyst was recovered from these scale-up reactions and able to be recycled without compromising yield or enantioselectivity.

Experimental Information

General Information

All ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Unity Plus 500 MHz spectrophotometer at ambient temperature in $CDCl_3$. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Low resolution mass spectrometry data was obtained on an Agilent LC/MSD VL system by electrospray (ESI) flow injection analysis in the positive mode. Mobile phases were water and acetonitrile with 0.1% formic acid. The MS settings were: voltage = 3000V, fragmentor = 70 and chamber temperature = 350 °C. UPLC-MS analysis was performed on a C18 column (1.7mm, 2.1 X 50 mm) with CH_3CN:H_2O gradient as eluent with UV, ELSD and electrospray ionization (ESI) positive ion detection. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]_D$ (concentration in grams/100mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC System with a diode array detector. Chiral columns include Chiralcel®OD (Chiral Technologies Inc., 25cm x 4.6mm I.D.), Chiralpak®AD-H (Chiral Technologies Inc., 25cm x 4.6mm I.D.) and (*R,R*)-Whelk-O (Regis®Technologies Inc., 25cm x 4.6mm I.D.).

Procedure for the Asymmetric Preparation of (S)-2-((bis(4-methoxyphenyl)methyl)amino)-2-(4-methoxyphenyl)ethan-1-ol ***(2.63)***

An oven dried reaction tube was charged with a stir bar and to it was added boronic acid (0.20 g, 1.3 mmol), glycolaldehyde dimer (0.060 g, 0.50 mmol), DAM amine (0.24 g, 1.0 mmol), (*S*)-Br_2BINOL (0.0089 g, 0.02 mmol), and 3Å M.S. (500 mg). The reaction was equipped with a rubber septum, kept under Ar, and to it was added ethanol (2.5 mL). The reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and dissolved in a small amount of diethyl ether. The solution was transferred to a 250 mL separatory funnel and to it was added 75 mL 2M KOH and 40 mL dichloromethane. The organic layer was extracted and the aqueous layer washed twice more with DCM. The organic layers were pooled, dried over Na_2SO_4 and concentrated under reduced pressure to yield the product. The product was further purified over a silica plug with 10% – 30% ethyl acetate/hexanes to yield the pure product as an orange oil (0.287 g, 73%). **er =** >99:1. $\mathbf{[\alpha]_D}$ = +46.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 10 Hz, 2H), 7.20 (d, *J* = 10 Hz, 2H), 7.14 (d, *J* = 5 Hz, 2H), 6.90 (d, *J* = 10 Hz, 2H), 6.86 (d, *J* = 10 Hz, 2H), 6.80 (d, *J* = 5 Hz, 2H), 4.62 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.67 – 3.61 (overlap, 2H), 3.56 (dd, *J* = 10, 5 Hz, 1H), 2.05 (s, NH), 1.26 (dd, *J* = 5, 5 Hz, OH). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 159.22, 158.67, 137.11, 135.13, 132.53, 132.37, 128.75, 128.47, 128.24, 127.98, 114.25, 114.13, 113.96, 113.92, 113.59, 67.06, 62.13, 60.85, 55.42, 55.40, 55.38. **MS** (FIA) *m/z* calc'd for $[C_{24}H_{27}NO_4+Na]^+$ 416.19, found 416.2.

General Procedure for the Asymmetric Preparation of β-amino Alcohols ***2.66 – 2.69, 2.73, 2.78 – 2.83***

An oven dried reaction tube was charged with a stir bar and to it was added boronic acid (1.3 mmol), glycolaldehyde dimer (0.060 g, 0.50 mmol), DAM amine (0.24 g, 1.0 mmol), (*S*)-Br_2BINOL (0.022 g, 0.05 mmol), and 3Å M.S. (500 mg). The reaction was equipped with a rubber septum, kept under Ar, and to it was added ethanol. The reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and dissolved in a small amount of diethyl ether. The solution was transferred to a 250 mL separatory funnel and to it was added 75 mL 2M KOH and 40 mL dichloromethane. The organic layer was extracted and the aqueous layer washed twice more with DCM. The organic layers were pooled, dried over Na_2SO_4 and concentrated under reduced pressure to yield the product. If needed, the product was further purified over a silica plug with 10% – 30% ethyl acetate/hexanes. The racemic version was performed under the same conditions with (±)-BINOL as the catalyst.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-((bis(4-methoxyphenyl)methyl)amino)ethan-1-ol ***(2.66)***

This compound was prepared according to the general procedure using benzo[*d*][1,3]dioxol-5-ylboronic acid (0.22 g, 1.3 mmol) and 2.5 mL ethanol to afford to product as a yellow oil (0.289 g, 71%). **er** = 98:2. $\mathbf{[\alpha]_D}$ = +72.4° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 10 Hz, 2H), 7.24 (d, *J* = 5 Hz, 2H), 6.96 (d, *J* = 10 Hz, 1H), 6.88 (d, *J* = 10 Hz, 2H), 6.81 – 6.79 (overlap, 3H), 6.70 (d, *J* = 5 Hz,

1H), 5.98 (s, 2H), 4.68 (s, 1H), 3.89 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.69 (m, 1H), 3.61 (m, 1H), 1.43 (s, NH), 1.26 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 158.81, 158.68, 148.17, 147.17, 137.01, 135.08, 134.60, 128.75, 128.24, 120.80, 114.15, 113.95, 108.55, 107.49, 101.20, 67.09, 62.12, 61.27, 55.41. **MS** (FIA) *m/z* calc'd for $[C_{24}H_{25}NO_5+Na]^+$ 430.17, found 430.0

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-4-phenylbut-3-en-1-ol ***(2.67)***

This compound was prepared according to the general procedure using trans-2-styreneboronic acid (0.19 g, 1.3 mmol) and 2.5 mL ethanol to afford to product as a yellow oil (0.305 g, 78%). **er** = 98:2. **$[\alpha]_D$** = +63.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.38 – 7.35 (overlap, 2H), 7.33 – 7.30 (overlap, 5H), 7.27 (d, J = 10 Hz, 2H), 6.87 (d, J = 10 Hz, 2H), 6.81 (d, J = 10 Hz, 2H), 6.44 (d, J = 18 Hz, 1H), 6.01 (dd, J = 18, 8 Hz, 1H), 4.93 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.66 (m, 1H), 3.50 (dd, J = 10, 10 Hz, 1H), 3.33 (m, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.50, 158.71, 137.13, 135.47, 132.76, 129.49, 128.62, 128.25, 127.98, 127.71, 126.32, 114.17, 114.04, 113.92, 65.45, 62.34, 59.65, 58.61, 55.40, 30.46. **MS** (FIA) m/z calc'd for $[C_{25}H_{27}NO_3+Na]^+$ 412.20, found 412.1.

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-5-phenylpent-3-en-1-ol ***(2.68)***

This compound was prepared according to the general procedure using (E)-(3-phenylprop-1-en-1-yl)boronic acid (0.21 g, 1.3 mmol) and 2.5 mL ethanol to afford to product as a yellow oil (0.333, 82%). **er** = >99:1. **$[\alpha]_D$** = +20.5° (c = 1.0, $CHCl_3$). **^{1}H**

NMR (500 MHz, Chloroform-d) δ 7.33 (dd, J = 13, 8 Hz, 2H), 7.24 – 7.19 (overlap, 7H), 6.83 (d, J = 5 Hz, 2H), 6.81 (d, J = 5 Hz, 2H), 5.70 (ddd, J = 15, 5, 5 Hz, 1H), 5.34 (dd, J = 15, 5 Hz, 1H), 4.87 (s, 1H), 3.76 (s, 3H), 3.58 (dd, J = 10, 5 Hz, 1H), 3.42 – 3.38 (overlap, 3H), 3.15 (m, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.69, 140.26, 137.05, 135.33, 133.44, 130.18, 128.60, 128.54, 128.23, 126.29, 114.08, 114.00, 65.31, 62.31, 59.19, 55.36, 39.02. **MS** (FIA) m/z calc'd for $[C_{26}H_{29}NO_3+Na]^+$ 426.20, found 426.1.

(S)-2-((bis(4-methoxyphenyl)methyl)amino)-2-(3,4-dimethoxyphenyl)ethan-1-ol ***(2.69)***

This compound was prepared according to the general procedure using 3,4-dimethoxyphenylboronic acid (0.24 g, 1.3 mmol) and 1.0 mL ethanol to afford to product as a dark oil (0.335 g, 79%). **er** = 96:4. **$[\alpha]_D$** = +41.8° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.25 (d, J = 10 Hz, 2H), 7.20 (d, J = 10 Hz, 2H), 6.87 – 6.86 (overlap, 3H), 6.80 (d, J = 5 Hz, 2H), 6.76 (d, J = 10 Hz, 1H), 6.73 (s, 1H), 4.64 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.66 – 3.64 (overlap, 2H), 3.58 (dd, J = 10, 10 Hz, 2H), 2.51 (s, NH), 1.54 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.75, 158.64, 149.25, 148.53, 137.06, 135.09, 133.11, 128.70, 128.25, 119.46, 114.07, 113.91, 111.41, 111.50, 67.04, 62.17, 61.31, 56.01, 55.34. **MS** (FIA) m/z calc'd for $[C_{25}H_{29}NO_5+Na]^+$ 446.20, found 446.2.

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-4-(4-methoxyphenyl)but-3-en-1-ol ***(2.73)***

This compound was prepared according to the general procedure using (E)-(4-methoxystyryl)boronic acid (0.23 g, 1.3 mmol) and 1.0 mL ethanol to afford to product as an oil (0.370 g, 88%). **er =** 93:7. **$[\alpha]_D$** = +89.7° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.48 (d, J = 10 Hz, 3H), 7.44 (d, J = 10 Hz, 3H), 7.04 (d, J = 10 Hz, 2H), 7.02 (d, J = 5 Hz, 2H), 6.99 (d, J = 5 Hz, 2H), 6.56 (d, J = 15 Hz, 1H), 6.03 (dd, J = 15, 10 Hz, 1H), 5.10 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 3.81 (dd, J = 10, 5 Hz, 1H), 3.65 (dd, J = 10, 10 Hz, 1H), 3.45 (m, 1H), 1.61 (s, NH), 1.43 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.50, 158.71, 137.13, 135.47, 132.76, 129.49, 128.62, 128.25, 127.98 127.71, 126.32, 114.17, 114.04, 113.92, 64.45, 62.34, 59.65, 58.61, 55.40, 30.46. **MS** (FIA) m/z calc'd for $[C_{26}H_{29}NO_4+Na]^+$ 442.20, found 442.2.

(S)-2-(4-methoxyphenyl)-2-(phenylamino)ethan-1-ol ***(2.78)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), aniline (0.093 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.172 g, 71%). **er =** 90:10. **$[\alpha]_D$** = +34.6° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.28 (dd, J = 10, 10 Hz, 2H), 7.11 (dd, J = 8, 8 Hz, 2H), 6.88 (d, J = 10 Hz, 2H), 6.68 (dd, J = 5, 5 Hz, 1H), 6.58 (d, J = 10 Hz, 2H), 4.47 (dd, J = 5, 5 Hz, 1H), 3.92 (dd, J = 13, 5 Hz, 1H), 3.79 (s, 3H), 3.74 (dd, J = 13, 5 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.20, 147.27, 131.98, 129.43, 129.29, 127.45, 118.11, 115.26, 114.39, 114.12, 67.51, 59.53, 55.41. **UPLC-MS** (ESI+) m/z calc'd for $[C_{15}H_{17}NO_2+H]^+$ 244.13, found 244.

(S)-2-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)ethan-1-ol ***(2.79)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), anisidine (0.12 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.229 g, 84%). **er =** >97:3. $\mathbf{[\alpha]_D}$ = +36.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.27 (d, J = 10 Hz, 2H), 6.87 (d, J = 10 Hz, 2H), 6.70 (d, J = 10 Hz, 2H), 6.54 (d, J = 10 Hz, 2H), 4.39 (dd, J = 8, 5 Hz, 1H), 3.89 (dd, J = 10, 5 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.70 (dd, J = 10, 8 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 139.94, 132.90, 129.55, 128.62, 128.56, 126.28, 116.60, 114.91, 65.25, 59.24, 55.88, 38.84. **MS** (FIA) m/z calc'd for $[C_{16}H_{19}NO_3+H]^+$ 274.14, found 274.2.

(S)-2-((2-bromophenyl)amino)-2-(4-methoxyphenyl)ethan-1-ol ***(2.80)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), 2-bromoaniline (0.17 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.225 g, 70%). **er =** 99:1. $\mathbf{[\alpha]_D}$ = -44.0° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.43 (dd, J = 7.9, 1.5 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.01 (ddd, J = 8.2, 7.3, 1.5 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.54 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H), 6.44 (dd, J = 8.2, 1.5 Hz, 1H), 5.12 (d, J = 4.5 Hz, NH), 4.52 (ddd, J = 4.5, 4.4, 4.2 Hz, 1H), 3.95 (ddd, J = 9.8, 7.7, 4.4 Hz, 1H), 3.81 (ddd, J = 9.8, 6.4, 4.2 Hz, 1H), 3.78 (s, 3H), 1.74 (dd, J = 6.7, 6.4 Hz, OH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.23, 144.11, 132.43, 131.33, 128.40, 127.81, 118.40, 114.41, 113.07,

110.45, 67.49, 59.30, 55.37. **UPLC-MS** (ESI+) m/z calc'd for $[C_{15}H_{16}BrNO_2+H]^+$ 322.04, found.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-(phenylamino)ethan-1-ol ***(2.81)***

This compound was prepared according to the general procedure using benzo[d][1,3]dioxol-5-ylboronic acid (0.22 g, 1.3 mmol), aniline (0.09 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.194 g, 75%). **er =** 94:6. $\mathbf{[\alpha]_D}$ = +19.5° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.12 (dd, J = 8.7, 7.4 Hz, 2H), 6.88 – 6.82 (overlap, 2H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (tt, J = 7.4, 1.1 Hz, 1H), 6.57 (dd, J = 8.7, 1.1 Hz, 2H), 5.94 (dd, J = 6.9, 1.6 Hz, 2H), 4.41 (dd, J = 7.0, 4.2 Hz, 1H), 3.90 (dd, J = 11.1, 4.2 Hz, 1H), 3.72 (dd, J = 11.1, 7.0 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 148.23, 147.22, 147.12, 134.21, 129.24, 120.00, 118.02, 113.93, 108.64, 107.11, 101.17, 67.55, 59.72. **UPLC-MS** (ESI+) m/z calc'd for $[C_{15}H_{15}NO_3+H]^+$ 258.11, found.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-((4-methoxyphenyl)amino)ethan-1-ol ***(2.82)***

This compound was prepared according to the general procedure using benzo[d][1,3]dioxol-5-ylboronic acid (0.22 g, 1.3 mmol), anisidine (0.12 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.209 g, 73%). **er =** 96:4. $\mathbf{[\alpha]_D}$ = +35.4° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 6.85 (d, J = 1.7 Hz, 1H), 6.82 (dd, J = 8.0, 1.7 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.9 Hz, 1H), 6.54 (d, J = 8.9 Hz, 1H), 5.93 (d, J = 4.2 Hz, 1H), 4.34 (dd, J = 7.5, 4.2 Hz, 1H), 3.87 (dd, J = 11.0, 4.2 Hz, 1H), 3.70 (s, 3H), 3.69 (dd, J = 11.0, 7.5 Hz, 1H). **^{13}C NMR** (125 MHz,

Chloroform-d) δ 152.53, 148.19, 147.08, 141.25, 134.39, 120.05, 115.39, 114.83, 108.61, 107.14, 101.15, 67.53, 60.73, 55.81. **UPLC-MS** (ESI+) m/z calc'd for $[C_{16}H_{17}NO_4+H]^+$ 288.12, found.

(S,E)-2-((4-methoxyphenyl)amino)-5-phenylpent-4-en-1-ol ***(2.83)***

This compound was prepared according to the general procedure using (E)-(3-phenylprop-1-en-1-yl)boronic acid (0.21 g, 1.3 mmol), anisidine (0.12 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.260 g, 92%). **er** = 94:6. $\mathbf{[\alpha]_D}$ = +17.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.27 – 7.24 (overlap, 2H), 7.19 (m, 1H), 7.09 (d, J = 10 Hz, 2H), 6.77 (d, J = 10 Hz, 2H), 6.65 (d, J = 10 Hz, 2H), 5.86 (ddd, J = 15, 5, 5 Hz, 1H), 5.45 (dd, J = 15, 5 Hz, 1H), 3.94 (dd, J = 10, 5 Hz, 1H), 3.76 (dd, J = 10, 5 Hz, 1H), 3.75 (s, 3H), 3.59 (dd, J = 10, 5 Hz, 1H), 3.37 (d, J = 5 Hz, 2H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 153.21, 139.94, 132.90, 129.55, 128.62, 128.56, 126.28, 116.60, 114.91, 65.25, 59.24, 55.88, 38.84. **MS** (FIA) m/z calc'd for $[C_{18}H_{21}NO_2+H]^+$ 284.16, found 284.3.

General Procedure for the Asymmetric Preparation of β-amino Alcohols ***2.70 – 2.72, 2.74, 2.87 – 2.93***

An oven dried reaction tube was charged with a stir bar and to it was added boronic acid (1.3 mmol), glycolaldehyde dimer (0.060 g, 0.50 mmol), amine (1.0 mmol), (*S*)-Br_2BINOL (0.044 g, 0.10 mmol), and 3Å M.S. (500 mg). The reaction was equipped with a rubber septum, kept under Ar, and to it was added ethanol (2.5 mL). The reaction

was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and dissolved in a small amount of diethyl ether. The solution was transferred to a 250 mL separatory funnel and to it was added 75 mL 2M KOH and 40 mL dichloromethane. The organic layer was extracted and the aqueous layer washed twice more with DCM. The organic layers were pooled, dried over Na_2SO_4 and concentrated under reduced pressure to yield the product. If needed, the product was further purified over a silica plug with 10% – 30% ethyl acetate/hexanes. The racemic version was performed under the same conditions with (±)-BINOL as the catalyst.

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-4-(3-(trifluoromethyl)phenyl)but-3-en-1-ol ***(2.70)***

This compound was prepared according to the general procedure using diethyl (E)-(3-(trifluoromethyl)styryl)boronate (0.65 mL, 2M in toluene, 1.3 mmol), DAM amine (0.24 g, 1.0 mmol), and 1.85 mL ethanol to afford to product as an oil (0.2841 g, 62%). **er** = 98:2. $\mathbf{[\alpha]_D}$ = +61.6° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.60 (s, 1H), 7.53 – 7.50 (overlap, 2H), 7.44 (dd, J = 15, 10 Hz, 1H), 7.31 (d, J = 5 Hz, 1H), 7.27 (d, J = 10, 2H), 6.88 (d, J = 5 Hz, 2H), 6.82 (d, J = 10 Hz, 2H), 6.48 (d, J = 12.5 Hz, 1H), 6.11 (dd, J = 12.5, 5 Hz, 1H), 4.90 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.72 – 3.67 (overlap, 2H), 3.52 (dd, J = 10, 10 Hz, 1H), 3.35 (m, 1H), 1.43 (s, NH), 1.26 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.84, 158.77, 137.48, 136.86, 135.35, 132.37, 131.70, 130.89, 129.68, 129.20, 128.56, 128.25, 124.36, 123.11, 114.20, 114.05, 113.59, 65.24, 62.61, 59.55, 55.39. **MS** (FIA) m/z calc'd for $[C_{26}H_{26}F_3NO_3+H]^+$ 458.19, found 458.3.

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-4-(thiophen-3-yl)but-3-en-1-ol ***(2.71)***

This compound was prepared according to the general procedure using diethyl (E)-(2-(thiophene-3-yl)vinyl)boronic acid (0.20 g, 1.3 mmol), DAM amine (0.24 g, 1.0 mmol), and 1.0 mL ethanol to afford to product as an oil (0.2928 g, 74%). **er** = 95:5. $\mathbf{[\alpha]_D}$ = +59° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.31 – 7.26 (overlap, 5H), 7.21 (d, J = 5 Hz, 1H), 7.15 (brs, 1H), 6.86 (d, J = 10 Hz, 2H), 6.80 (d, J = 10 Hz, 2H), 6.46 (d, J = 15 Hz, 1H), 5.85 (dd, J = 15, 10 Hz, 1H), 4.92 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.64 (dd, J = 10, 5 Hz, 1H), 3.47 (dd, J = 10, 10 Hz, 1H), 3.26 (m, 1H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.72, 139.40, 137.01, 135.41, 128.55, 128.22, 127.31, 126.25, 125.05, 122.33, 114.12, 113.98, 65.31, 62.33, 59.49, 55.34. **MS** (FIA) m/z calc'd for $[C_{23}H_{25}NO_3S+H]^+$ 395.16, found 333.1 $[M – (OCH_3)_2]^+$.

(S,E)-2-((bis(4-methoxyphenyl)methyl)amino)-4-(naphthalen-2-yl)but-3-en-1-ol ***(2.72)***

This compound was prepared according to the general procedure using diethyl (E)-(2-naphthalen-2-yl)vinyl)boronate (0.65 mL, 2M in toluene, 1.3 mmol), DAM amine (0.24 g, 1.0 mmol), and 1.85 mL ethanol to afford to product as an oil (0.3881 g, 88%). **er** = >98:2. $\mathbf{[\alpha]_D}$ = +74.5° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.82 – 7.79 (overlap, 3H), 7.71 (s, 1H), 7.58 (dd, J = 7.5, 2.5 Hz, 1H), 7.49 – 7.43 (overlap, 2H), 7.33 (d, J = 10 Hz, 2H), 7.28 (d, J = 10 Hz, 2H), 6.88 (d, J = 10 Hz, 2H), 6.81 (d, J = 10, 2H), 6.61 (d, J = 17.5 Hz, 1H), 6.13 (dd, J = 17.5, 7.5 Hz, 1H), 4.96 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.54 (dd, J = 10, 5 Hz, 1H), 3.48 (dd, J = 10, 5 Hz, 1H), 3.38 (m, 1H), 2.35 (s,

NH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.82, 158.74, 137.06, 135.45, 134.15, 133.69, 133.34, 133.18, 129.06, 128.63, 128.39, 128.27, 128.09, 127.81, 126.51, 126.11, 123.59, 114.20, 114.06, 65.40, 62.49, 59.73, 55.39. **MS** (FIA) m/z calc'd for $[C_{29}H_{29}NO_3+H]^+$ 440.21, found 440.1.

(S)-2-((bis(4-methoxyphenyl)methyl)amino)-2-(4-(dimethylamino)phenyl)ethan-1-ol ***(2.74)***

This compound was prepared according to the general procedure using diethyl 4-(dimethylamino)phenylboronate (0.65 mL, 2M in toluene, 1.3 mmol), DAM amine (0.24 g, 1.0 mmol), and 1.85 mL ethanol to afford to product as an oil (0.3623 g, 89%). **er =** >99:1. **$[\alpha]_D$** = +84° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.28 (d, J = 5 Hz, 2H), 7.22 (d, J = 10 Hz, 2H), 7.09 (d, J = 10 Hz, 2H), 6.87 (d, J = 10 Hz, 2H), 6.81 (d, J = 5 Hz, 2H), 6.74 (d, J = 10 Hz, 2H), 4.68 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.64 – 3.61 (overlap, 2H), 3.56 (dd, J = 15, 10 Hz, 1H), 2.97 (s, 6H), 2.95 (s, NH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 158.68, 158.56, 150.20, 137.28, 135.26, 129.13, 128.75, 128.23, 128.11, 128.01, 116.70, 114.30, 113.87, 112.77, 67.03, 62.01, 60.76, 55.31, 40.67. **MS** (FIA) m/z calc'd for $[C_{25}H_{30}N_2O_3+Na]^+$ 429.20, found 429.2.

(S)-2-(4-methoxyphenyl)-2-morpholinoethan-1-ol ***(2.87)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), morpholine (0.087 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.188 g, 79 %). **er =** >96:4. **$[\alpha]_D$** = +10.1° (c =

1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.13 (d, J = 8 Hz, 2H), 6.89 (d, J = 8, 2H), 3.94 (dd, J = 10, 5 Hz, 1H), 3.81 (s, 3H), 3.74 – 3.65 (overlap, 5H), 3.58 (dd, J = 10, 5, 1H), 2.57 – 2.53 (overlap, 2H), 2.41 – 2.34 (overlap, 2H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.47, 130.59, 130.04, 127.83, 113.84, 69.89, 67.36, 60.34, 55.39 **MS** (FIA) m/z calc'd for $[C_{13}H_{19}NO_3+H]^+$ 238.14, found 238.2.

(S)-2-(dibenzylamino)-2-(4-methoxyphenyl)ethan-1-ol ***(2.88)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid **3a** (0.20 g, 1.3 mmol), dibenzylamine (0.20 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.277 g, 80%). **er =** >95:5. **$[\alpha]_D$** = +53.5° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.27 – 7.26 (overlap, 8H), 7.21 – 7.17 (overlap, 2H), 7.11 (d, J = 10 Hz, 2H), 6.88 (d, J = 10 Hz, 2H), 4.03 (dd, J = 13, 13 Hz, 1H), 3.85 – 3.81 (overlap, 3H), 3.77 (s, 3H), 3.50 (dd, J = 13, 8 Hz, 1H), 3.06 (d, J = 15 Hz, 2H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.43, 140.47, 139.28, 130.51, 129.11, 128.69, 128.52, 128.27, 127.37, 127.09, 127.06, 113.84, 62.43, 60.67, 55.40, 53.58, 53.31. **MS** (FIA) m/z calc'd for $[C_{23}H_{25}NO_2+H]^+$ 348.19, found 348.2.

(S)-2-(4-methoxyphenyl)-2-(methyl(phenyl)amino)ethan-1-ol ***(2.89)***

This compound was prepared according to the general procedure using 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), N-methylaniline (0.11 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.177 g, 67%). **er =** 87:13. **$[\alpha]_D$** = +128.1° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.27 (ddd, J = 8.9, 7.3, 0.8 Hz,

2H), 7.05 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.86 – 6.79 (overlap, 3H), 5.04 (dd, J = 9.5, 5.3 Hz, 1H), 4.13 – 4.06 (overlap, 2H), 3.78 (s, 3H), 2.67 (s, 3H), 2.15 (s, OH). **^{13}C NMR** (125 MHz, Chloroform-d) δ 159.03, 151.31, 129.32, 128.42, 122.47, 118.52, 115.14, 113.97, 64.33, 61.67, 55.32, 31.90. **UPLC-MS** (ESI+) m/z calc'd for $[C_{16}H_{19}NO_2+H]^+$ 258.14, found 258.2.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-(dibenzylamino)ethan-1-ol ***(2.90)***

This compound was prepared according to the general procedure using benzo[d][1,3]dioxol-5-ylboronic acid (0.22 g, 1.3 mmol), dibenzylamine (0.20 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.199 g, 55%). **er** = 95:5. **$[\alpha]_D$** = +102.8° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.35 – 7.34 (overlap, 8H), 7.29 – 7.24 (overlap, 2H), 6.86 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.71 (dd, J = 7.9, 1.7 Hz, 1H), 6.01 (dd, J = 3.8, 1.5 Hz, 2H), 4.05 (dd, J = 10.7, 10.5 Hz, 1H), 3.91 (d, J = 13.4 Hz, 2H), 3.86 (dd, J = 10.5, 5.3 Hz, 1H), 3.82 (s, OH), 3.57 (dd, J = 10.7, 5.3 Hz, 1H), 3.17 (d, J = 13.4 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 147.82, 147.36, 139.14, 129.04, 128.91, 128.68, 128.53, 128.31, 127.37, 127.13, 122.91, 109.35, 108.25, 101.24, 62.85, 60.72, 53.57. **UPLC-MS** (ESI+) m/z calc'd for $[C_{23}H_{23}NO_3+H]^+$ 362.17, found.

(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-(methyl(phenyl)amino)ethan-1-ol ***(2.91)***

This compound was prepared according to the general procedure using benzo[d][1,3]dioxol-5-ylboronic acid (0.22 g, 1.3 mmol), N-methylaniline (0.11 g, 1.0

mmol), and 2.5 mL ethanol to afford to product as an oil (0.181 g, 67%). **er** = 91:9. **$[\alpha]_D$** = + (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.26 (m, 2H), 6.94 (d, J = 8.2 Hz, 2H), 6.83 (tt, J = 7.3, 1.0 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.65 – 6.57 (overlap, 2H), 5.93 (s, 2H), 4.99 (dd, J = 9.4, 5.3 Hz, 1H), 4.11 – 4.01 (overlap, 2H), 2.84 (s, OH), 2.70 (s, 3H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 151.05, 147.93, 147.03, 131.27, 129.37, 120.36, 118.70, 115.12, 108.34, 107.86, 101.13, 64.71, 61.81, 32.05.

UPLC-MS (ESI+) m/z calc'd for $[C_{16}H_{17}NO_3+H]^+$ 272.12, found.

(S,E)-2-morpholino-5-phenylpent-3-en-1-ol ***(2.92)***

This compound was prepared according to the general procedure using (E)-(3-phenylprop-1-en-1-yl)boronic acid (0.21 g, 1.3 mmol), morpholine (0.09 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0. g, 81%). **er** = 93:7. **$[\alpha]_D$** = -73.4° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.30 (m, 2H), 7.22 (m, 1H), 7.17 (m, 2H), 5.81 (dddd, J = 15.4, 6.7, 6.7, 0.7 Hz, 1H), 5.44 (dddd, J = 15.3, 8.9, 1.5, 1.5 Hz, 1H), 3.79 – 3.64 (overlap, 4H), 3.56 – 3.51 (overlap, 2H), 3.42 – 3.38 (overlap, 2H), 3.09 (ddd, J = 8.8, 8.8, 5.8 Hz, 1H), 2.68 (ddd, J = 10.6, 5.8, 3.1 Hz, 2H), 2.45 (ddd, J = 9.6, 5.9, 3.0 Hz, 2H). ^{13}C NMR (125 MHz, Chloroform-d) δ 139.75, 135.65, 128.63, 128.60, 126.34, 125.33, 68.07, 67.28, 66.54, 60.62, 39.19. **UPLC-MS** (ESI+) m/z calc'd for $[C_{15}H_{21}NO_2+H]^+$ 248.16, found.

(S,E)-2-(dibenzylamino)-5-phenylpent-4-en-1-ol ***(2.93)***

This compound was prepared according to the general procedure using (E)-(3-phenylprop-1-en-1-yl)boronic acid (0.21 g, 1.3 mmol), dibenzylamine (0.20 g, 1.0 mmol), and 2.5 mL ethanol to afford to product as an oil (0.320 g, 90%). **er** = 82:18. $\mathbf{[\alpha]_D}$ = +48° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.27 – 7.14 (overlap, 15H), 5.71 (ddd, J = 15, 8, 8 Hz, 1H), 5.45 (dd, J = 15, 10 Hz, 1H), 3.80 (d, J = 15 Hz, 2H), 3.73 (s, 2H), 3.56 (dd, J = 10, 10 Hz, 1H), 3.39 (dd, J = 5, 5 Hz, 1H), 3.34 (dd, J = 10, 5 Hz, 1H), 3.28 (d, J = 15 Hz, 2H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 140.02, 139.21, 136.06, 129.12, 128.69, 128.63, 128.56, 128.37, 127.35, 126.40, 124.95, 61.33, 61.15, 53.62, 53.12, 39.37. **MS** (FIA) m/z calc'd for $[C_{25}H_{27}NO+H]^+$ 358.21, found 358.4.

Procedure for the Determination of Absolute Stereochemistry

To a 250 mL RBF was added (*S*)-2-((bis(4-methoxyphenyl)methyl)amino)-2-(4-methoxyphenyl)ethan-1-ol (0.34 g, 0.86 mmol). To the flask was added 6M HCl in water (86 mL, 516 mmol) and the reaction was allowed to reflux for 24 hours with stirring. The reaction was then cooled to room temperature and to it was added 2M NaOH in water to a pH of ~13. The solution was extracted thrice with DCM (~50 mL) and the organic layers pooled, dried over Na_2SO_4, and concentrated on the rotovap. The resultant oil was analyzed by optical rotation to determine absolute stereochemistry. $\mathbf{[\alpha]_D}$ = +26° (c = 1.0, $CHCl_3$) {lit = +22.6° (c = 1.0, EtOH)}[59]. The purity was determined by NMR, and the spectral data is in agreement with the literature.

Procedure for the Direct Inject Mass Spectrometry Study

An oven dried reaction tube was charged with a stir bar and to it was added 4-methoxyphenylboronic acid (0.20 g, 1.3 mmol), morpholine (0.087 g, 1.0 mmol), glycolaldehyde dimer (0.060 g, 0.50 mmol), (*S*)-Br_2BINOL (0.044 g, 0.10 mmol), and 3Å M.S. (500 mg). The reaction was equipped with a rubber septum, kept under Ar, and to it was added ethanol (2.5 mL). The reaction was stirred at room temperature for 2 h and an aliquot was removed and diluted with acetonitrile to a concentrated of 0.5 – 1.0 mg/mL. From this was removed 10 μL which was further diluted to a final volume of 1 mL with acetonitrile. The sample was analyzed by direct inject mass spectrometry on a MicroMassZQ 2000 *via* syringe pump (150 mL/min) with electropspray ionization in negative mode (ESI^-, ES/voltages: capillary 3.01 KV, cone 60 V. Temperature: source 130 °C, desolvation 260 °C. Gas flow: desolvation 250 L/h. Pump flow: 60 μL/min).

CHAPTER THREE. Reactivity of Electron Deficient Boronates in the Petasis Reaction

Introduction

The methodology described in Chapter Two to synthesize chiral β-amino alcohols *via* the Petasis reaction demonstrates the first catalytic asymmetric Petasis reaction of glycolaldehyde to access amino alcohols. Upon investigating the generalization of this method, we found halogenated aromatic boronic acids and boronates were not useful reaction partners. In addition to narrowing the scope of the reaction, this lack of reactivity decreased the ability to further functionalize the reaction products. With the addition of a halogen on the aromatic ring in our products, we envisioned the possibility of their use as cross-coupling reaction partners. In an effort to increase the chemical utility of our methodology, we set out to optimize the reaction to include electron-deficient boronates.

Two specific compounds represent the utility of incorporating halogenated boronates in the Petasis reaction, and thus our motivation for this methodology improvement. The first, (*S*)-clopidogrel, is a compound marketed by Bristol-Myers Squibb (BMS) and Sanofi as Plavix for the treatment of heart disease[62]. Clopidogrel is an ADP receptor antagonist and has antithrombotic and antiagreggatory properties at IC_{50}'s of 1.8 and 0.53 μM, respectively. The most recent process route for the synthesis of (*S*)-clopidogrel bisulfate was reported in 2007[63]. The synthesis begins with racemic amino acid **3.1**, which is first converted to the acid chloride and esterified to give **3.2** (Figure 3.1). This amino ester is then chirally resolved with L-(+)-tartaric acid to obtain the

desired stereocenter. Following resolution, the amine is functionalized *via* substitution of tosylate **3.4** to give **3.5** as the HCl salt. Subjecting the salt to acidic conditions in the presence of paraformaldehyde provided (*S*)-clopidogrel as the bisulfate salt, **3.6**.

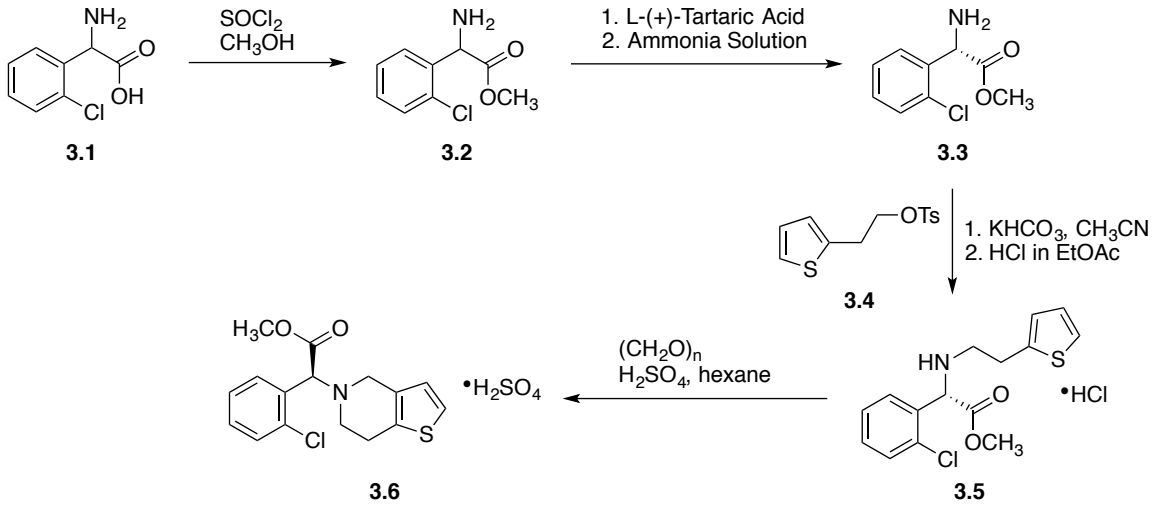


Figure 3.1. Process route for the synthesis of (*S*)-clopidogrel

While this process is highly scalable, with 35 Kgs of the final product being isolated, there are two major drawbacks. First, the amino substitution from **3.3** to **3.5** proceeds over 40 hours. Second, and more importantly, the chiral resolution step takes between 45 and 50 hours to achieve the desired level of enantiomeric purity, and results in half of the material being disposed of. Implementing asymmetric multi-component reactions (MCRs) would address both the atom and step economy issues of this route.

In 2008, Kalinski demonstrated three MCRs that could be used to access clopidogrel[64]. The first is a 3-component Ugi reaction (Figure 3.2) between cyclohexenyl isocyanide **3.7**, aldehyde **3.8**, and amine **3.9**. Hydrolysis of the resulting secondary amino amide to the corresponding amino acid with THF and HCl gives **3.10**. Following

esterification with methanol and acid, (±)-clopidogrel is obtained in 73% yield over 3 steps.

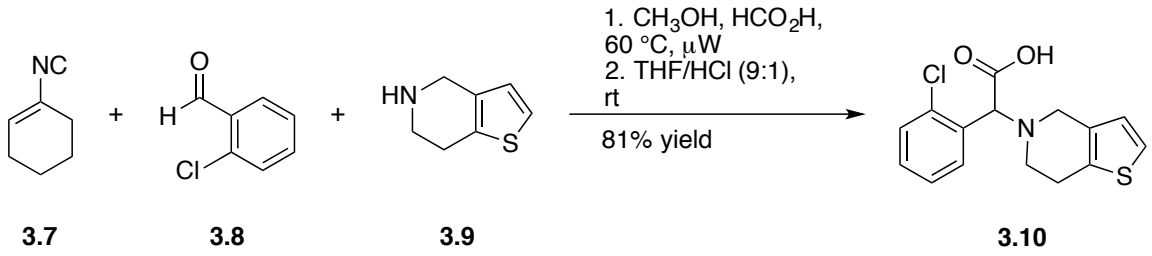


Figure 3.2. Ugi synthesis of clopidogrel

An alternative 3-component Ugi reaction was also demonstrated, using a different isocyanide (Figure 3.3). In this method, isocyanide **3.11** is used and the methyl ester can be isolated directly from hydrolysis of the Ugi product. Although one step shorter than the previous Ugi reaction, the overall yield is much lower at 22% over two steps. The authors postulate that this is due to the instability of the isocyanide and its partial decomposition during the MCR.

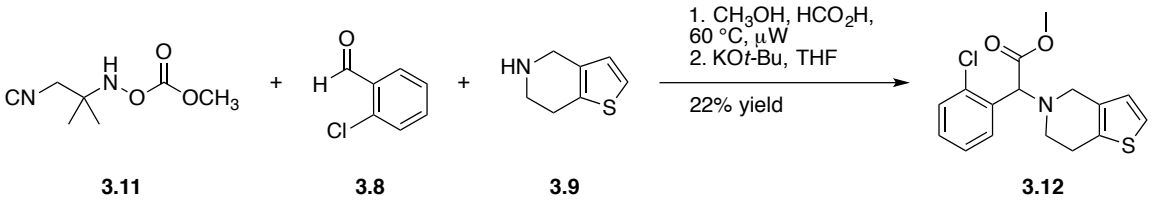
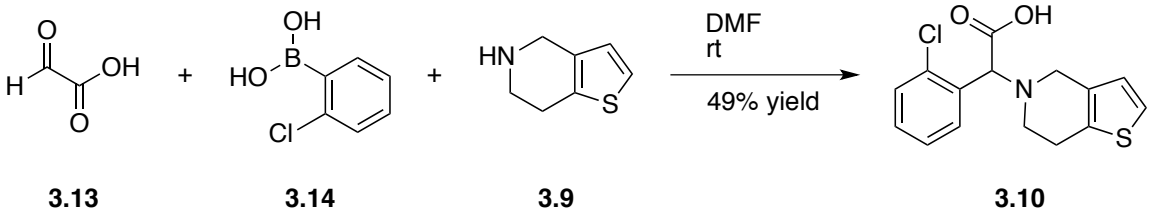


Figure 3.3. Alternative Ugi synthesis of clopidogrel

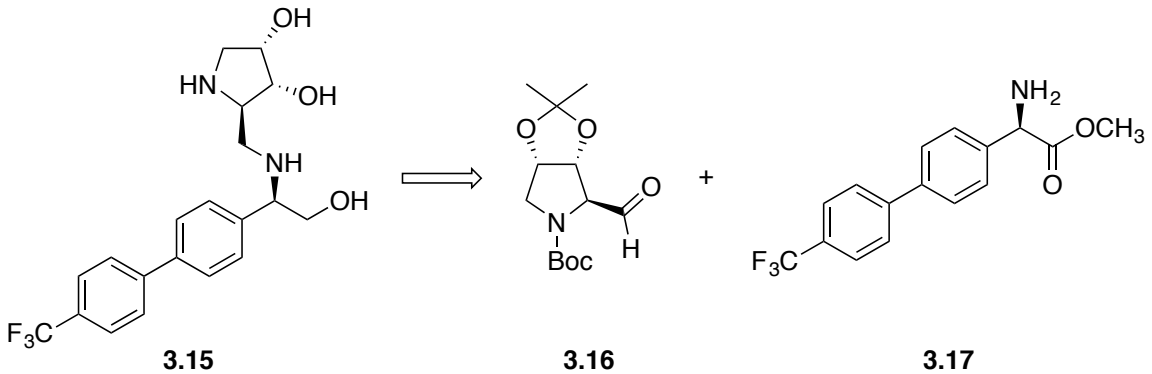
Finally, a Petasis approach was employed to access clopidogrel (Figure 3.4). Glyoxylic acid **3.13** was coupled with *ortho*-chlorophenylboronic acid **3.14** and secondary amine **3.9** to give free amino acid **3.10**. This intermediate was then esterified in the same way as the hydrolyzed Ugi product to produce **3.12**. This method, though one step shorter than the Ugi route, was less efficient, yielding only 44% over two steps.



3.13 **3.14** **3.9** **3.10**

Figure 3.4 Petasis synthesis of clopidogrel

The second compound of interest is β-amino alcohol **3.15** reported by the National Cancer Research Institute in Genoa, Italy to have activity against hematological and solid malignancies[34] (Figure 3.5). Compound **3.15** exhibits μM IC_{50} potency against nine different cancel cell lines, including lung cancer, T cell leukemia, and four breast cancer cell lines. Bello and co-workers show a synthesis of this molecule from amino



3.15 **3.16** **3.17**

Figure 3.5. Retrosynthesis of amino alcohol 3.15

aldehyde **3.16** and amino ester **3.17**. The amino aldehyde is synthesized in 7 steps from a D-gulonic acid lactone, and the amino ester from commercially available 4-hydroxyphenyl glycine in 5 steps. From **3.16** and **3.17**, only 3 steps remain in the synthesis: reductive amination coupling, reduction of the ester, and global deprotection of the acetal and Boc group.

Imagining a multicomponent approach to this synthesis, a number of steps could be cut out of the synthesis. A Petasis reaction between aryl boronic acid **3.18**, glycolaldehyde **3.19**, and dibenzylamine **3.20** would provide the β-amino alcohol core in one step (Figure 3.6). From here, 3 transformations, including one deprotection, provide compound **3.24**. This intermediate leads to the desired product following TFA deprotection. Although still utilizing the 6-step amino aldehyde from Bello's method, the number of steps to get to the reductive amination partner is cut down from 5 to 3. Additionally, the resultant 1,2-diamine is already at the desired oxidation state, so the LAH ester reduction step can also be eliminated from the synthesis.

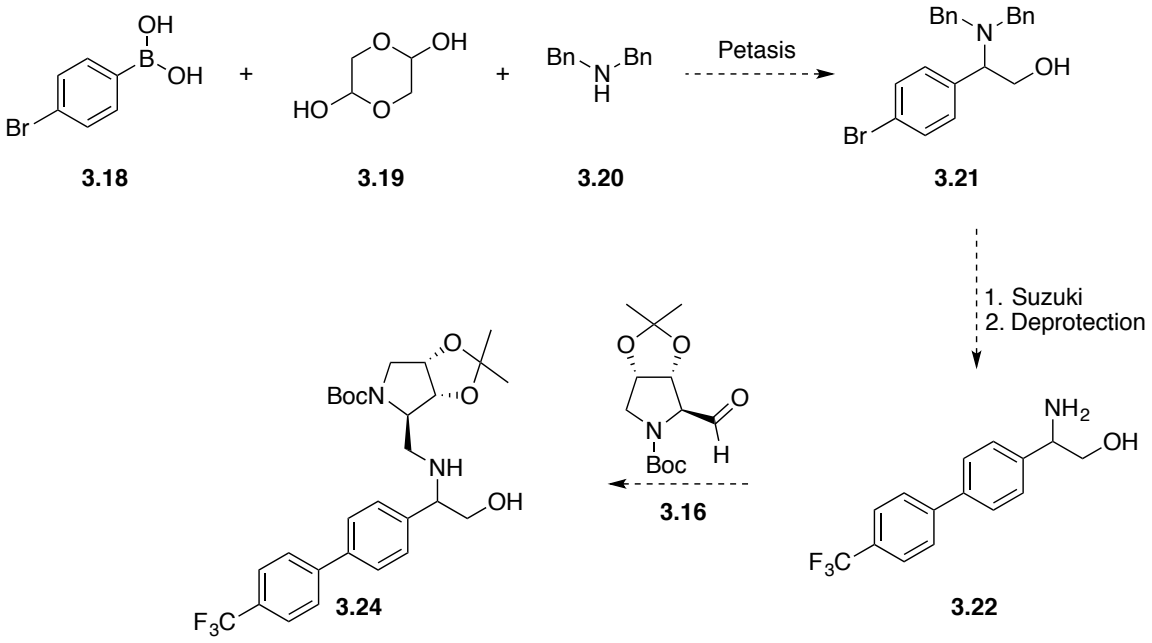


Figure 3.6. Proposed MCR route to amino alcohol 3.15

As demonstrated above, MCR routes to biologically active compounds can be beneficial when it comes to atom, step, and time economy. In the examples provided, halogens are either present in the final product, or needed as a reactive handle for further

diversification to obtain the product after the MCR step. Being able to include halogenated aromatic boronic acid substrates in our previously designed Petasis methodology would expand its utility and allow for broader applications of the reaction.

Background

Observed Reactivity of Electron-Deficient Boronates

To better understand why electron-deficient halogenated boronates behaved so poorly in our methodology, we first looked at Petasis reactions that observed this desired reactivity. Nicos Petasis first reported the synthesis of α-arylglycines *via* his newly discovered boronic acid Mannich reaction[65]. In this method, the reaction of glyoxylic acid, a primary amine, and an aryl boronic acid provides the amino acid product (Figure 3.7). The reactivity of boronic acids was general, as electron-rich, -neutral, and -deficient boronic acids all provided the desired products in moderate to good yields. Notably,

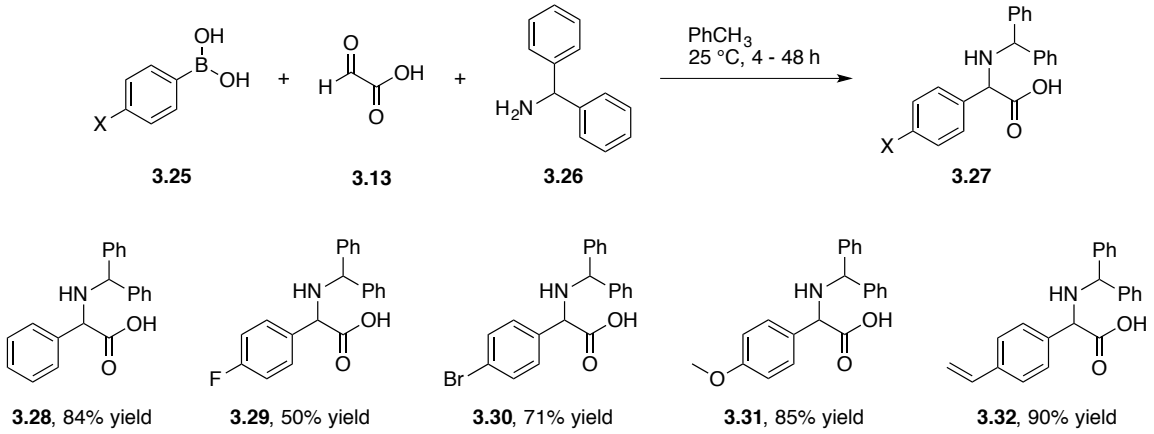


Figure 3.7. Petasis reaction of aryl boronates with diphenylmethylamine

while *p*-bromophenyl boronic acid and *p*-fluoroboronic acid did participate in the reaction, their yields were lower than those of their electron-rich counterparts. The more electronegative fluorine substituent gave the lowest yielding amino acid, **3.29**, at 50%.

The Whittaker later published a similar reaction for accessing amino acids with glyoxylic acid[66]. In this method, they report using microwave irradiation to promote and accelerate the Petasis reaction between glyoxylic acid, aryl boronic acids, and morpholine

(Figure 3.8). After optimization by a design of experiments (DOE) approach, they determined that the reaction proceeded best at 120 °C, for 10 minutes, 1M in DCM. They also found isolation of the Petasis products to be easier upon conversion to the methyl ester. The provided aryl α-amino esters were isolated in moderate yields and showed a tolerance for electronically and sterically diverse substitutions on the boronic acid.

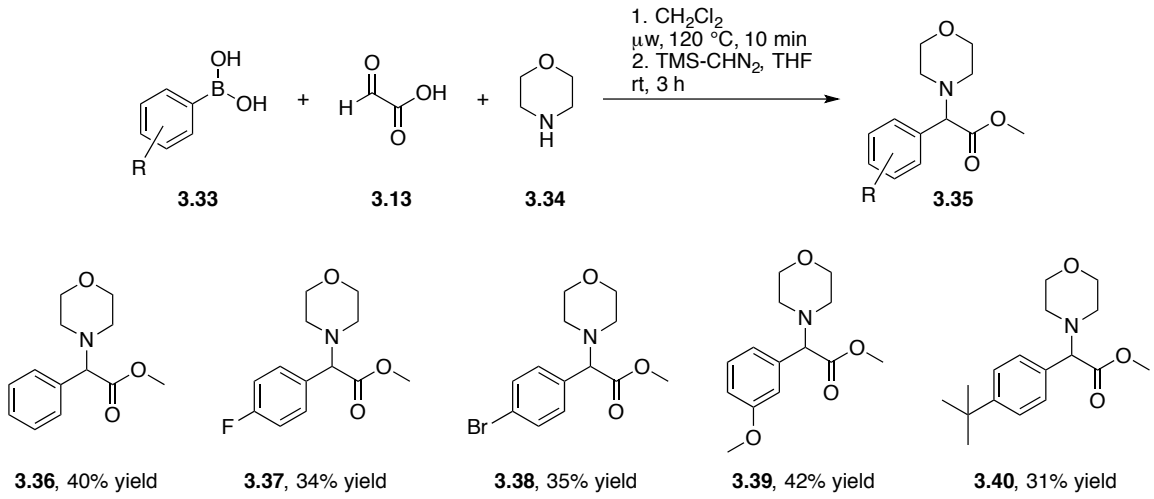


Figure 3.8. Microwave-assisted Petasis reaction of glyoxylic acid

B. Wesley Trotter also developed a diastereoselective Petasis reaction of glyoxylic acid in 2005 that also incorporated halogenated aryl boronic acids[67]. In this method, racemic 2-methylpyrrolidine **3.42** was employed as the amino component of the reaction with aryl boronic acids, and dr's of up to >95:5 *anti*:*syn* were achieved (Figure 3.9). The reaction was shown to be amenable to electron-neutral and -rich aromatic boronic acids. Halogenated substrates also worked in the transformation, giving yields of 83% and 71% (**3.45** and **3.46**). But largely electron-withdrawing groups like nitriles shut

down the reactivity (**3.47**), which is likely due to the boronic acid's inherently lower nucleophilicity.

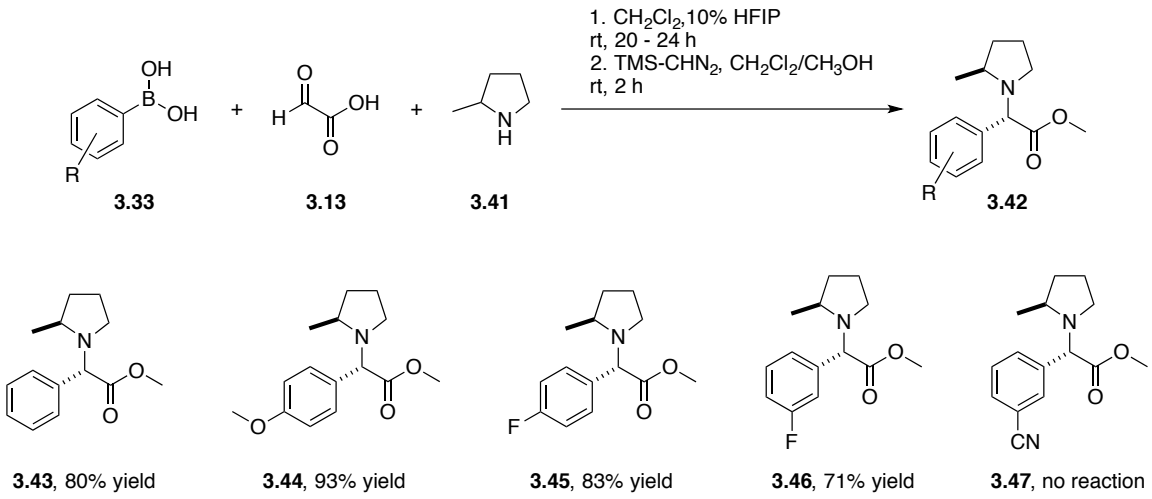


Figure 3.9. Diastereoselective Petasis reaction of glyoxylic acid

In addition to the methods that incorporate electron-poor boronic acids in the Petasis reaction with glyoxylic acid, the Li group reported their inclusion in the scope of nucleophiles in a Petasis reaction of imino amides[68]. Aromatic boronic acids **3.25** and prepared imino benzyl- or methylamide **3.48** react in DCE with heating at 100 °C to produce aryl amino amides **3.49** as products (Figure 3.10). Ranging in yield from 65% to

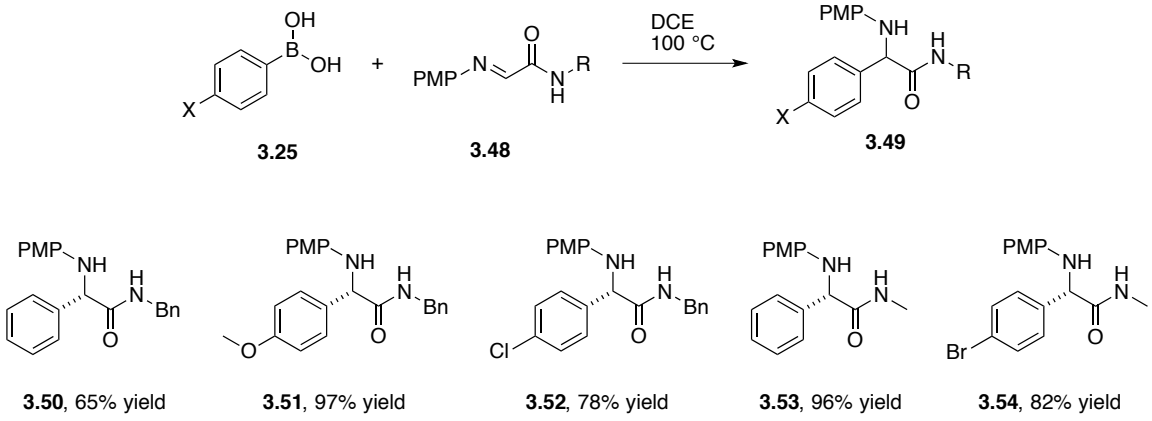


Figure 3.10. Petasis reaction of imino amides

97%, electronically variant boronic acids add into both the imino benzylamide and imino methylamide equally well. The highest yielding boronate nucleophile is *p*-methoxy substituted at 97% (**3.51)**, and the lowest is surprisingly unsubstituted phenylboronic acid when coupled with the imino N-benzylamide, providing **3.50** is 65% yield. This method demonstrates another system in which halogenated aryl boronates participate as reaction partners in the Petasis reaction.

Another example came from Mandal in 2008[69], with a slight variation. This work highlights the use of indoles as the amine component, with tertiary indoles giving the best results. In this Petasis-like methodology, the indole acts as a carbon nucleophile, with the 3-position adding into the glyoxylic acid aldehyde. 1,4-addition of the boronate into the newly formed α,β-unsaturated imine would give way to carboxylic acids 3.56 (Figure 3.11). Under refluxing dioxane conditions, electron-rich methoxy and methylthio boronic acids provided access to **3.57** and **3.58** in 60% yield and 49% yield, respectively. Similarly, *p*-fluoro and -bromo substitutions on the boronate produced **3.59** and **3.60** in 42% and 48% yields.

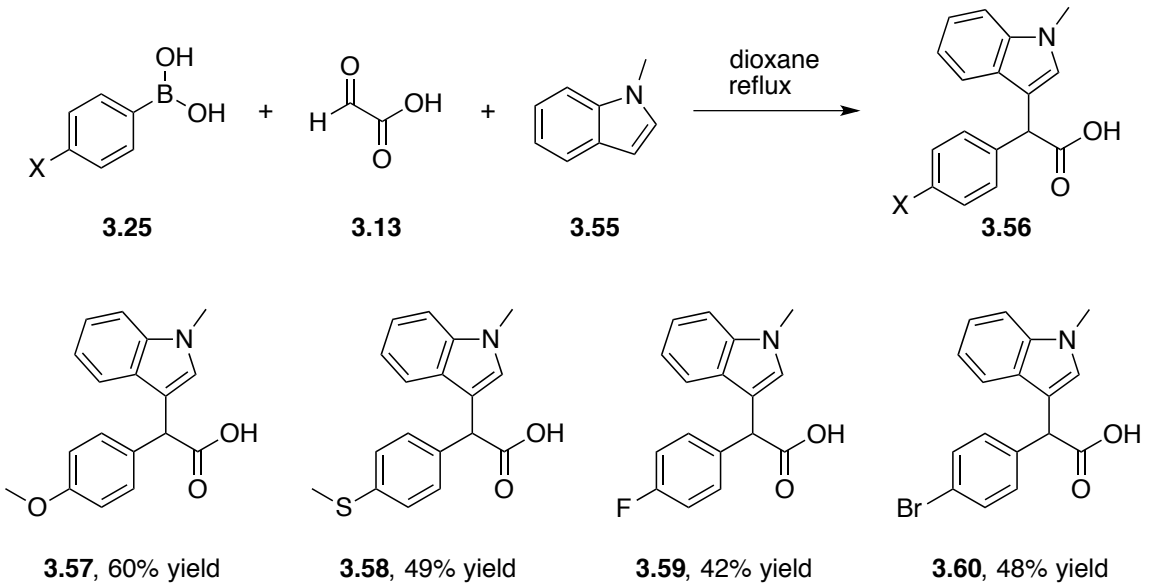


Figure 3.11. Petasis reaction of N-methylindole

All of the aforementioned methods have two things in common. They all show that halogenated phenylboronic acids can and do participate in the Petasis reaction, and they all contain electron-deficient aldehydes. In most of the cases, glyoxylic acid was used as the aldehyde, and the presence of the α-carboxylic acid will inductively pull electron density away from the aldehyde, and subsequent imine intermediate, making it inherently more electrophilic. In the one example that doesn't use glyoxylic acid, the imine is pre-formed and has a pendant amide group, providing the same effect as the carboxylic acid in glyoxylate. When the aldehyde lacks this α-withdrawing group, a shift in reactivity is observed.

Decreased Reactivity of Electron-Deficient Boronates

In a report published in 2010, Yu's group demonstrated that salicylaldehyde was a viable reaction partner with morpholine and aromatic boronic acids in the Petasis

reation[70]. Using solvent-free conditions at 80 °C for 2 hours, amino phenols **3.62** were isolated as reaction products (Figure 3.12). All of the substrates illustrated here provided their corresponding products in ~90% yield, regardless of their electronic properties.

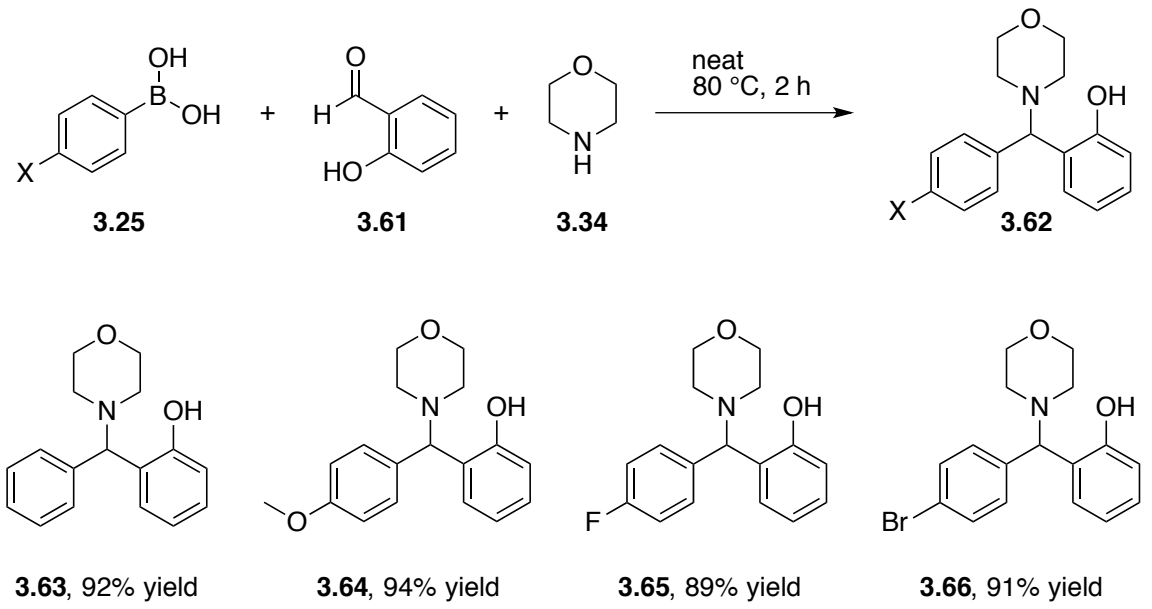


Figure 3.12. Solvent free Petasis reaction of salicylaldehyde

In conjunction with their study of glyoxylic acid, Whittaker and co-workers also investigated the Petasis reaction of salicylaldehyde, **3.61**[66] (Figure 3.13). Under the same microwave irradiation conditions with morpholine, **3.34**, the desired amino phenol products were observed. Phenylboronic acid provided **3.68** in 76% yield and *m*-methoxyphenylboronic acid gave **3.69** in 62% yield, while *p*-fluorophenylboronic acid produced amino phenol **3.70** with 75% yield. Although salicylaldehyde lacks an electron-withdrawing group, a Brønsted acidic intramolecular hydrogen bond can be formed between the aldehyde and phenol, facilitating imine formation. Additionally, the only amine shown to work in this methodology is morpholine. In fact, Whittaker points out that the secondary amine is crucial for observing this reactivity. When determining

the reactivity of electron-neutral phenylboronic acid with salicylaldehyde, only the imine could be isolated when primary amines were utilized; no Petasis coupling product was detected in those cases. This observation would prove to be very important in our own optimizations for electron-deficient boronates.

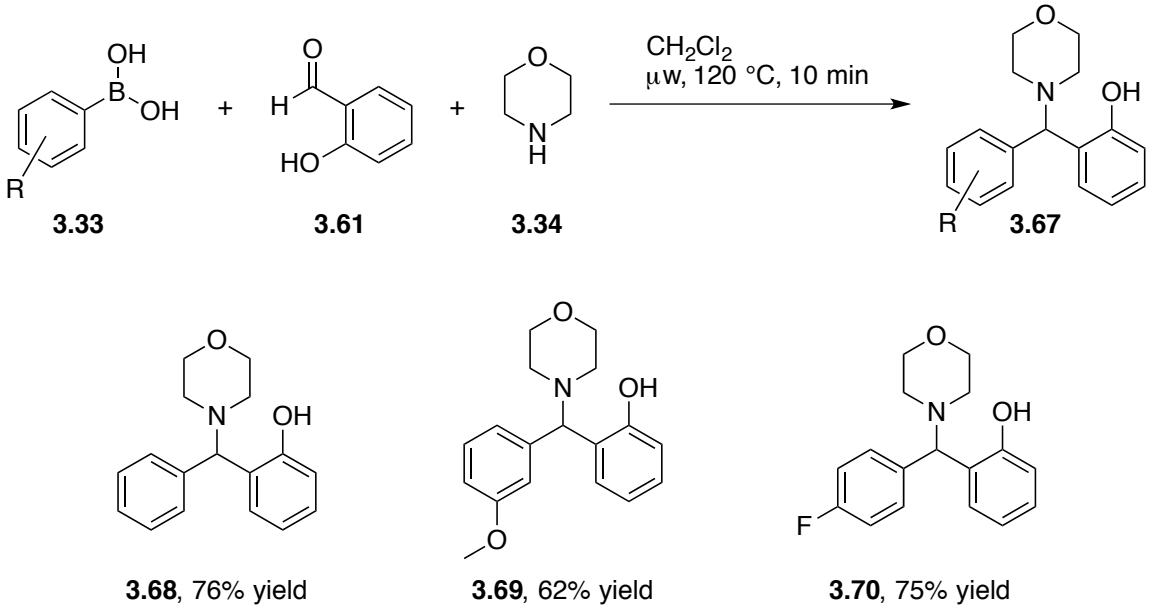


Figure 3.13. Microwave Petasis reaction of salicylaldehyde

A resin-to-resin transfer reaction (RRTR) developed by Kim Thompson and Dennis Hall was shown to incorporate electron-deficient boronates. In the RRTR, solid-supported boronate **3.71**, glyoxylic acid, and resin-bound amine **3.72** were heated at 65 °C to give α-amino acid **3.73**[71] (Figure 3.14). Although this transformation provided some electron-rich amino acids in yields greater than 95%, *p*-bromophenylboronic acid failed to provide satisfactory results, producing the corresponding product at 21% conversion and 10% isolated yield.

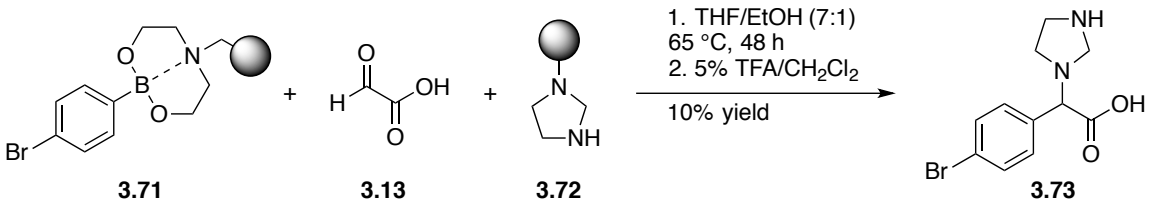


Figure 3.14. Resin-to-resin Petasis reaction

In another method that explored the use of electron-poor aromatic amines in the Petasis reaction, Hamley reported seeing low to negligible reactivity with electron-deficient boronates[72]. In the example highlighted below, the reaction of 2-aminopyridine with glyoxylic acid and *p*-chlorophenylboronic acid to produce aryl amino acid **3.76** was investigated under microwave irradiation conditions (Figure 3.15). These conditions

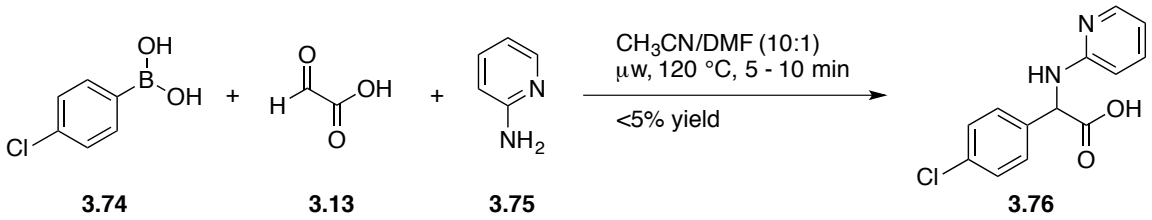


Figure 3.15. Petasis reaction of 2-aminopyridine

resulted in less than 5% yield of the desired product. Employing traditional heating at 82 °C for 0.5 – 4 hours did not appear to improve the observed reactivity. Switching to 3-aminopyridine, a slight enhancement in reactivity to 15% yield under microwave conditions was observed, but the conventional heating method remained equally unreactive. Additionally, the reaction with 2-aminopyrazine provided the same results as 2-aminopyridine, and inclusion of 2-aminopyrimidine led to isolation of the respective product in 12% yield for both heating methods. The authors note this low reactivity as the only major limitation to the methodology.

Based on current literature, we knew the task to incorporate electron-deficient halogenated aromatic boronates into our methodology would not be trivial. We began our investigations at a clear disadvantage to the existing methods; our aldehyde lacks the seemingly key feature of an α-withdrawing group. Keeping that in mind, we set out to determine the depth of this limitation. Herein, we report the study and optimization of electron deficient boronate nucleophiles in the catalytic asymmetric Petasis reaction of glycolaldehyde dimer.

Results and Discussion

Initial Findings with p-chlorophenylboronic acid

We began our studies with the examination of *p*-chlorophenylboronic acid in our standard reaction conditions (Figure 3.16). At 10 mol % catalyst loading of (*S*)-Br_2BINOL as a solution in ethanol with 3Å molecular sieves, we did not observe the

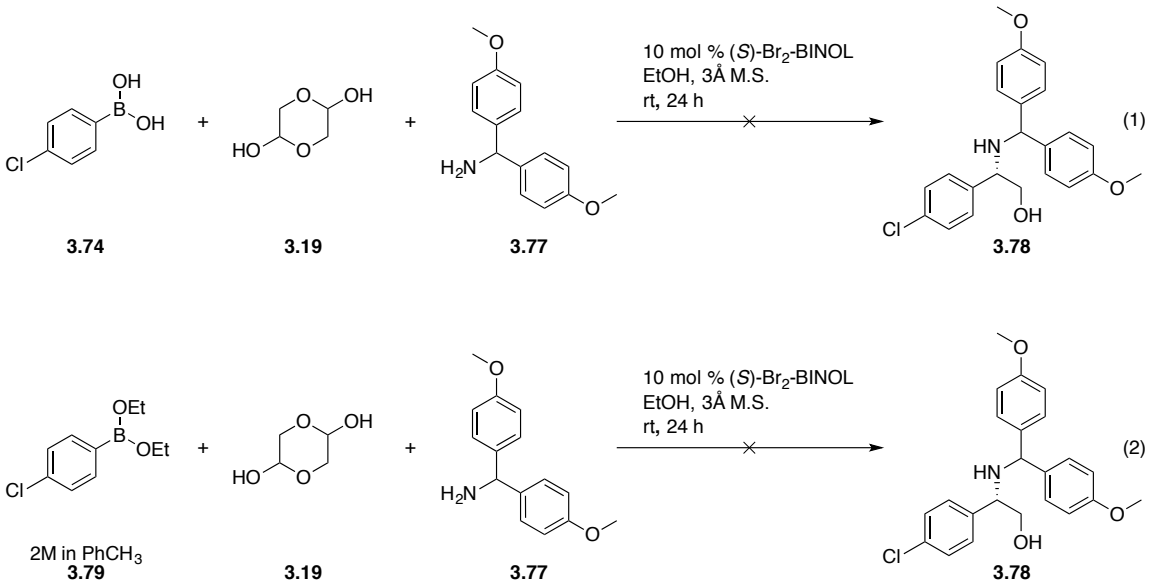
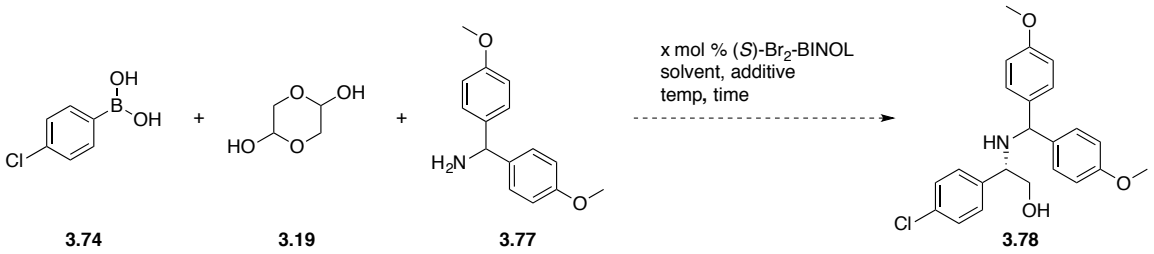


Figure 3.16. Examination of *p*-chlorophenylboronate in the Petasis reaction of glycolaldehyde

formation of our desired product, β-amino alcohol **3.78**. With this lack of reactivity, the boronic acid was substituted with diethyl boronate ester **3.79** to see if a faster catalyst exchange rate would have an effect on overall reactivity. Unfortunately, product was not able to be isolated in this case either. Because the previously optimized conditions did not work with this substrate, we turned our focus to screening conditions in an effort to observe any reactivity.

Condition Screening

Using the literature that exists on electron-deficient boronates in the Petasis reaction as a guide, we began investigating different reactions conditions for *p*-chlorophenylboronic acid. The results of these studies are summarized in Table 3.1. We looked into adjusting molar equivalents of starting materials, mol % catalyst loading,



3.74 **3.19** **3.77** **3.78**

	3.74:3.19:3.77	x	[3.77]	Solvent	Additive	Temp	Time	Result
1	1.3:0.5:1.0	20	1M	$PhCF_3$	3Å M.S.	rt	24 h	N.R.
2	1.3:0.5:1.0	10	0.5M	$PhCF_3$/ F_3-EtOH	3Å M.S.	rt	24 h	N.R.
3	3.0:0.5:1.0	10	1.3M	$PhCH_3$, cat TEA	3Å M.S.	μW 300W	30 min	N.R.
4	1.0:1.0:1.0	10	0.2M	*t*-Amyl-OH	3Å M.S.	40 °C	24 h	N.R.
5	1.0:1.0:1.0	10	0.2M	*t*-Amyl-OH	---	40 °C	24 h	N.R.
6	1.3:0.5:1.0	20	0.2M	DCE	3Å M.S.	100 °C	5 h	N.R.
7	1.3:0.5:1.0	10	0.2M	DCM/HFIP	3Å M.S.	35 °C	24 h	N.R.
8	1.3:0.5:1.0	10	1M	DCM/HFIP	3Å M.S.	40 °C	24 h	N.R.
9	1.3:0.5:1.0	20	0.2M	DCM/HFIP	3Å M.S.	rt	24 h	N.R.
10	3.0:0.5:1.0	20	0.2M	DCM/HFIP	3Å M.S.	rt	24 h	N.R.
11	3.0:0.5:1.0	20	0.2M	DCM/HFIP	---	rt	24 h	N.R.
12	1.0:0.75:1.0	10	0.2M	DCM/HFIP	3Å M.S.	rt	24 h	N.R.
13	1.3:0.5:1.0	10	0.4M	HFIP	3Å M.S.	rt	24 h	N.R.

Table 3.1. Condition screen for the Petasis reaction with *p*-chlorophenylboronic acid

reaction concentration, solvent, additives, temperature, and time. Concerning solvent choice, we investigated both coordinating and non-coordinating solvents for their effect on the reaction. While coordinating solvents like alcohols could help with the exchange of our boronic acid with the diol catalyst, they could also occupy boron's empty *p*-orbital,

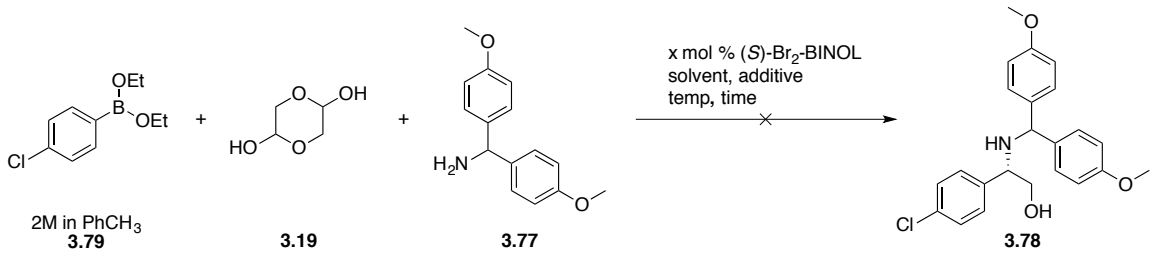
slowing down coordination of the hemiaminal with the boronic acid. To circumvent this coordinative saturation of boron, solvents lacking heteroatoms like O and N can be used. Non-coordinating trifluorotoluene did not improve the reaction, and mixing $PhCF_3$ with coordinating (and therefore exchanging) trifluoroethanol also had no effect (Table 3.1, entries 1 and 2). Attempting to accelerate the reaction through microwave irradiation while increasing the equivalents of the boronic acid to be in a 3:1 excess over the imine did not lead to the observation of product (entry 3). Additionally, gently heating the reaction in a bulkier alcohol solvent showed no reaction (entries 4 and 5).

In an attempt to adopt reaction conditions that have shown reactivity with halogenated boronates,[67,68] we evaluated both DCE and DCM/HFIP as solvents for the reaction. At 20 mol % catalyst, the reaction did not proceed in dichloroethane with 5 hours of heating at 100 °C (Table 3.1, entry 6). Using 10 mol % (*S*)-Br_2BINOL in DCM with 10% hexafluoroisopropanol added with mild heating of 35 °C resulted in no product formation, and increasing the concentration to 1M and temperature to 40 °C did not appear to have an effect (entries 7 and 8). The DCM/HFIP solvent mixture was evaluated for a few other conditions with increased catalyst loading and equivalents of boronate to no avail. Finally, HFIP was used on its own based on its previously reported ability to accelerate the Petasis reaction, but still no product was seen (entry 13).

At this stage, we turned our attention to the diethyl boronate as a reaction partner. Due to its more labile ethoxy ligands, we know that it would exchange faster with our BINOL catalyst, but that the substrate is also exceptionally moisture sensitive; exposure to humidity will hydrolyze the boronate back to boronic acid. For this reason, the diethyl

ester is stored as a solution in an air tight crimp vial. As the concentration and solvent can differ for storage, the following condition screening has been separated into tables based on the boronate used.

The first boronate investigated was a 2M solution in toluene (Table 3.2). This boronate was examined in 13 different reaction conditions, again varying equivalents, mol % catalyst, concentration, solvent, additive, temperature, and time. We started with trifluorotoluene as our solvent and assessed catalyst loadings from 5 mol % - 20 mol %



	3.79:3.19:3.77	x	[3.77]	Solvent	Additive	Temp	Time	Result
1	1.3:0.5:1.0	5	0.32M	$PhCF_3$	3Å M.S.	rt	24 h	N.R.
2	1.0:0.75:1.0	10	1M	$PhCF_3$	3Å M.S.	rt	24 h	N.R.
3	1.3:0.5:1.0	10	1M	$PhCF_3$	3Å M.S.	30 °C	24 h	N.R.
4	1.3:0.5:1.0	10	1M	$PhCF_3$	3Å M.S.	40 °C	24 h	N.R.
5	1.3:0.5:1.0	20	1M	$PhCF_3$	3Å M.S.	rt	24 h	N.R.
6	1.3:0.5:1.0	20	1M	$PhCF_3$	3Å M.S.	40 °C	5 h	N.R.
7	1.3:0.5:1.0	5	1.5M	$PhCH_3$	3Å M.S.	μW 20W	3 h	N.R.
8	1.3:0.5:1.0	10	1.5M	$PhCH_3$	3Å M.S.	30 °C	24 h	N.R.
9	1.3:0.5:1.0	10	1.5M	$PhCH_3$	---	30 °C	48 h	N.R.
10	1.3:0.5:1.0	10	1M	DCM/HFIP	3Å M.S.	30 °C	24 h	N.R.
11	1.3:0.5:1.0	20	0.2M	DCM/HFIP	3Å M.S.	rt	24 h	N.R.
12	1.3:0.5:1.0	20	0.2M	DCM/HFIP	3Å M.S.	30 °C	24 h	N.R.
13	1.3:0.5:1.0	5	0.1M	DCM	3Å M.S.	rt	24 h	N.R.

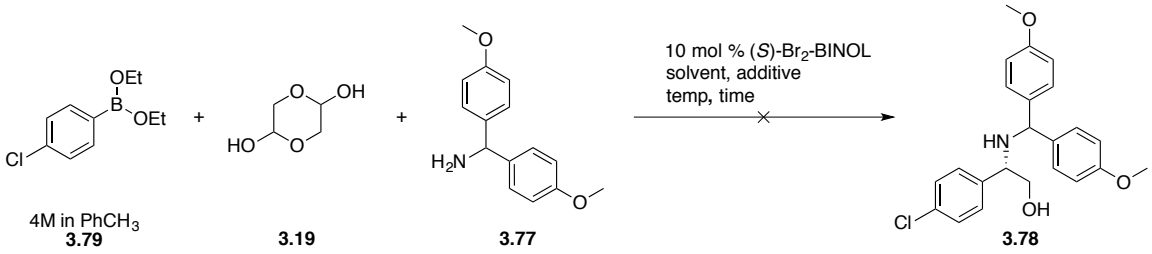
Table 3.2. Condition screen with diethyl boronate, 2M in $PhCH_3$

(entries 1 – 6). At room temperature, 30 °C, and 40 °C at a 1M concentration, the reaction did not appear to proceed to product. In toluene, neither microwave irradiation nor conventional heating in the presence or absence of molecular sieves worked to

promote the formation of product (entries 6 – 9). Lastly, the same DCM/HFIP solvent system that was evaluated with boronic acid did not provide detectable amounts of the desired product at any temperature or catalyst loading.

Diethyl boronate **3.79** as a 4M solution in toluene was next studied, and the conditions chosen are found in Table 3.3. This increase in boronate stock concentration provided neat reactions with lower total volume, allowing for higher increases in reaction concentration. Going back to DCE as a solvent choice, we looked at the reaction at 60° C both with and without molecular sieves and saw no product being formed (entries 1 – 2). Next we evaluated an acetonitrile/DCM solvent mixture under microwave conditions with set power and set temperature. In neither case was product able to be isolated. Using DCM alone also did not produce desired β-amino alcohol **3.78**. At this stage, we also changed the molecular sieves from 3Å to 4Å in an attempt to see if their size would have a significant impact on the observed lack of reactivity. However, both 3Å and 4Å M.S. performed equally poorly in the reaction (entries 6 and 7). At 1M and 2M concentrations of amine, DMF was investigated at room temperature and 40 °C, and gave no isolable product (entries 8 – 11). Looking into trifluorotoluene as the solvent at room temperature revealed that running the reaction at neither a concentration of 2M for 24 hours nor 0.8M for 48 hours could produce the product.

The remainder of the condition screens were done in toluene. The one reaction run at the standard molar equivalencies, entry 14, was done so at 3.1M in the microwave for 2 hours at 120 °C. At the highest evaluated concentration, no product was seen. Based on this observation, we increased the molar equivalents of



	3.79:3.19:3.77	[3.77]	Solvent	Additive	Temp	Time	Result
1	1.0:1.0:1.3	0.2M	DCE	4Å M.S.	60 °C	24 h	N.R.
2	1.0:1.0:1.3	0.2M	DCE	---	60 °C	24 h	N.R.
3	1.3:0.5:1.0	1M	ACN/DCM	3Å M.S.	µW 300W	10 min	N.R.
4	1.3:0.5:1.0	1M	ACN/DCM	3Å M.S.	µW 120 °C	10 min	N.R.
5	1.3:0.5:1.0	0.75M	DCM	3Å M.S.	µW 120 °C	10 min	N.R.
6	2.4:1.0:3.0	0.8M	DCM	3Å M.S.	rt	48 h	N.R.
7	2.4:1.0:3.0	0.8M	DCM	4Å M.S.	rt	48 h	N.R.
8	1.3:0.5:1.0	1M	DMF	3Å M.S.	rt	24 h	N.R.
9	1.3:0.5:1.0	1M	DMF	---	40 °C	24 h	N.R.
10	1.3:0.5:1.0	2M	DMF	3Å M.S.	rt	24 h	N.R.
11	1.3:0.5:1.0	2M	DMF	3Å M.S.	40 °C	24 h	N.R.
12	1.3:0.5:1.0	2M	$PhCF_3$	3Å M.S.	rt	24 h	N.R.
13	2.4:1.0:3.0	0.8M	$PhCF_3$	3Å M.S.	rt	48 h	N.R.
14	1.3:0.5:1.0	3.1M	$PhCH_3$	3Å M.S.	µW 120 °C	2 h	N.R.
15	3:1.0:1.0	1.3M	$PhCH_3$	3Å M.S.	rt	24 h	N.R.
16	3:0.5:1.0	1.3M	$PhCH_3$	3Å M.S.	rt	24 h	N.R.
17	3:0.5:1.0	1.3M	$PhCH_3$	3Å M.S.	30 °C	24 h	N.R.
18	3:0.5:1.0	1.3M	$PhCH_3$	3Å M.S.	30 °C	120 h	N.R.
19	3:1.0:1.0	1.3M	$PhCH_3$, cat TEA	3Å M.S.	40 °C	24 h	N.R.
20	3:0.5:1.0	1.3M	$PhCH_3$, cat TEA	3Å M.S.	60 °C	24 h	N.R.
21	3:0.5:1.0	1.3M	$PhCH_3$	3Å M.S.	4 °C	24 h	N.R.
22	3:0.5:1.0	1.3M	$PhCH_3$	3Å M.S.	µW 300W	30 min	N.R.

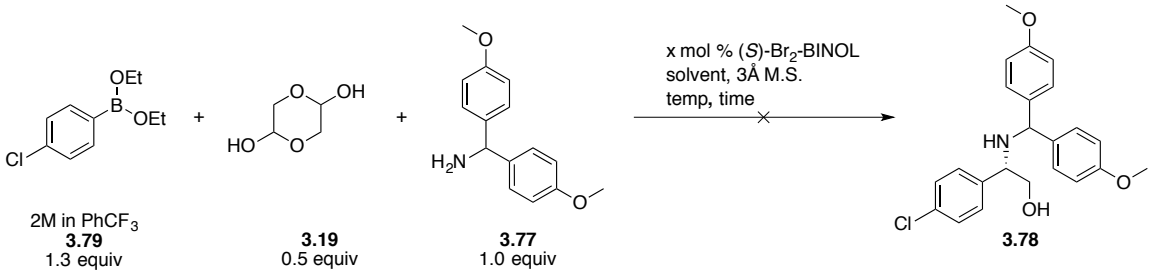
Table 3.3. Condition screen with diethyl boronate, 4M in $PhCH_3$

boronate to 3 and hoped that this could push the reaction towards product. As seen in entries 15 – 22, though, this was not the case. Regardless of temperatures at rt, 30 °C, 40

°C, 60 °C, and microwave irradiation, no product was able to be isolated, even after 120 hours (entry 18). The addition of catalytic amounts of triethylamine was proposed to help with ate complex formation and potentially render the boronate more nucleophilic, but this was not observed in the reactivity.

In most cases, when the reaction was allowed to run long enough, the solution turned black and only the boronate remains unreacted and a decomposition product was observed on the TLC baseline. This is thought to be from side reactions occurring with the amine, aldehyde, and *in situ* generated imine in the absence of a nucleophilic boronate. We thought by cooling the reaction down to 4 °C we would be able to slow down this exogenous process and potentially see Petasis product forming. Unfortunately, with a 3:1 molar ratio of boronate to imine at cold temperature, we still saw no product forming (Entry 21).

Our final broad condition screen was performed with a 2M solution of the diethyl boronate in trifluorotoluene (Table 3.4). Transitioning back to the 1.3:0.5:1.0 molar ratio of starting materials, we investigated a number of new solvents along with some of the previously tested ones. Among newly chosen solvents were NMP, trifluoroethanol, and heptafluorobutanol, and HFIP, DMF, and $PhCF_3$ were also screened. Again, we found that no conditions were suitable to promote the Petasis reaction of *p*-chlorophenylboronate.



	x	[3.77]	Solvent	Temp	Time	Result
1	10	1M	NMP	rt	24 h	N.R.
2	10	1M	DMF	rt	24 h	N.R.
3	10	1.7M	F_3-EtOH	rt	24 h	N.R.
4	20	1M	HFIP	rt	24 h	N.R.
5	20	1M	F_7-BuOH	rt	24 h	N.R.
6	10	0.5M	$PhCF_3$/EtOH	rt	24 h	N.R.
7	10	1.8M	$PhCF_3$	rt	24 h	N.R.
8	10	0.5M	$PhCF_3$	rt	24 h	N.R.
9	20	1M	$PhCF_3$	μW, 10W	30 min	N.R.
10	20	1M	$PhCF_3$	μW, 10W	1 h	N.R.

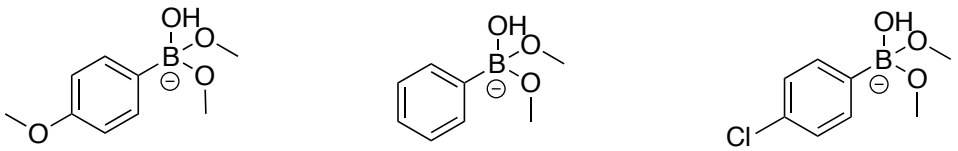
Table 3.4. Condition screen with diethyl boronate, 2M in $PhCF_3$

Calculations

With none of the reaction conditions we evaluated leading to the formation of product, we wanted to determine if this was due to the conditions we were trying, or to an underlying reactivity issue. In order to ascertain which was the cause, we began investigations into the energy levels of the nucleophilic reaction partner. We performed DFT calculations on three boronates: *p*-methoxyphenylboronic ester, phenylboronic ester, and *p*-chlorophenylboronic ester. We hoped to better understand the reactivity of halogenated boronates by gaining more information about the reactive orbitals of a boronate that participates extremely well in the reaction and comparing that to those that don't.

We began by simplifying the boronate to the dimethyl ester in order the decrease the complications that can arise by having too many rotatable bonds during energy

minimizations. Wanting to evaluate the nucleophilicity of the substrates, the ate complex was formed by addition of an extra OH group on the boronate. This gave **3.80**, **3.81**, and **3.82** as the compounds of interest for our DFT studies (Figure 3.17). These three boron-



3.80 **3.81** **3.82**

Figure 3.17. Boron-ate complexes for DFT calculations

ate complexes were chosen based on their relative reactivity in the Petasis reaction of glycolaldehyde, and are arranged in order of decreasing reactivity. The methoxy-substituted **3.80** behaves well in the reaction, leading to isolation of corresponding β-amino alcohol products in good yield. **3.81** exhibits minimal reactivity, and **3.82** shows none.

The DFT calculations were performed with a 6-31g** basis set, which defines which atoms are included in the calculations, and the B3LYP method, a hybrid functional theory[73]. Calculations were performed on energy-minimized structures using Jaguar, and energy levels for HOMO down to HOMO-10 were calculated. The calculated HOMOs for each of the complexes showed most of the electron density on the heteroatoms, likely due to their lone pairs (Figure 3.18). Additionally, based on these values, **3.81** has a higher calculated HOMO and should therefore be more reactive.

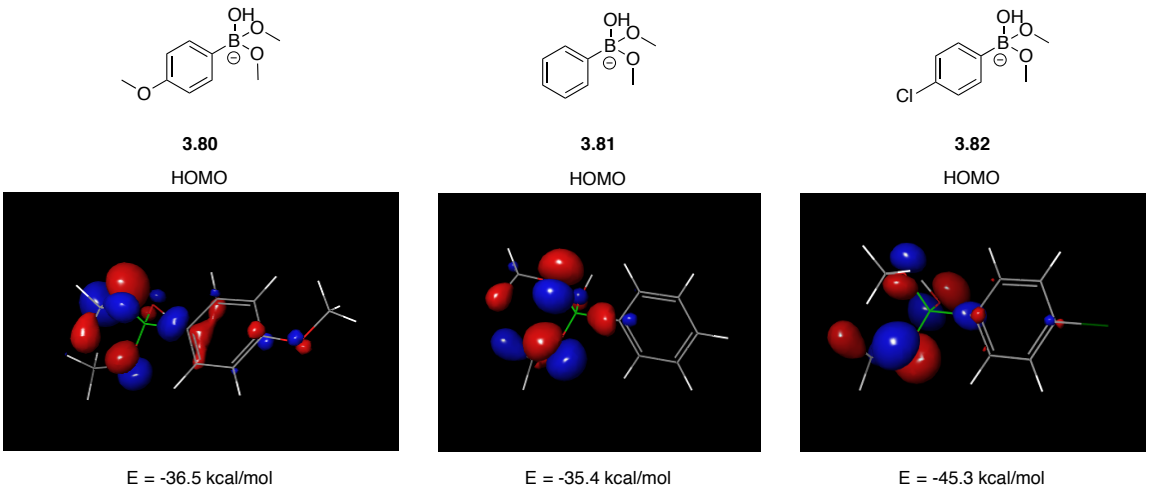


Figure 3.18. DFT-calculated HOMOs of boron-ate complexes

Knowing this is not true, and that the reactive complexes are nucleophilic at the boron-bonded carbon, energy levels lower than the calculated HOMO were assessed to find ones with electron density centered on the reactive carbon. In doing so, it was found that HOMO-2 for **3.80** and HOMO-3 for **3.81** and **3.82** showed electron density on the desired atom (Figure 3.19). It should also be noted that these energy levels most closely resembled the Hartree-Fock calculated HOMOs in both appearance and values. For this instance, the anticipated energy trend was observed, with **3.80** having the highest HOMO energy and **3.82** having the lowest. For these values, there is a roughly 5 kcal/mol energy difference between **3.80** and **3.81**, and around 14 kcal/mol energy difference between **3.80** and **3.81**. While this energy difference confirms the decreasing reactivity from electron-rich to electron-neutral to electron-deficient boronates, we were uncertain if it was a large enough difference to support a complete lack of reactivity with *p*-chlorophenylboronates.

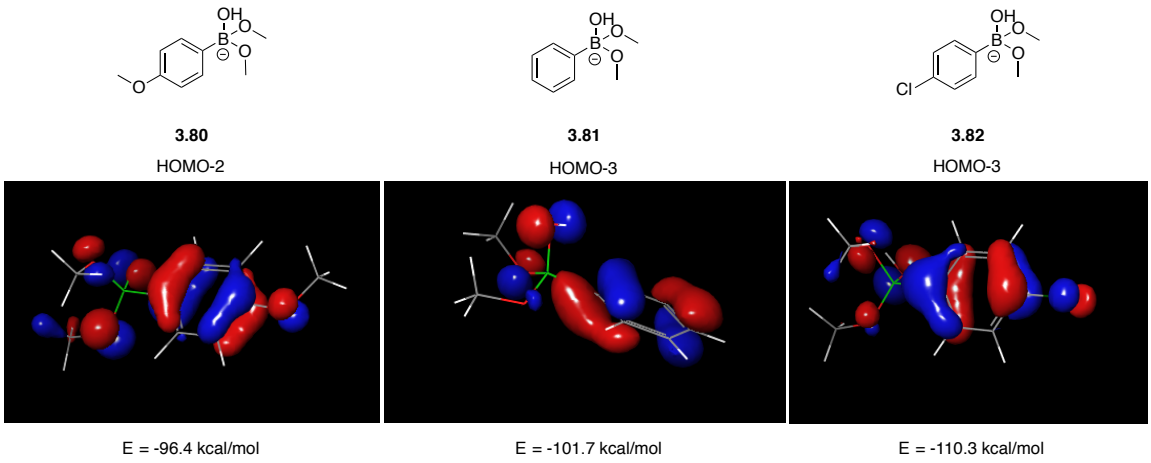
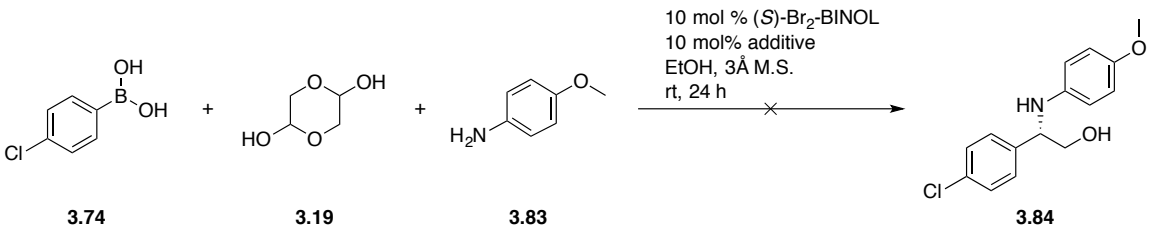


Figure 3.19. DFT-calculated reactive orbitals of boron-ate complexes

Additive Screen

Upon completion of calculations, the next goal became finding a way to either raise the HOMO of the boronate, or lower the LUMO of the imine. In order to do so, we examined different reaction additives. Because of material availability and cost economy, anisidine **3.83** was used as the primary amine for these studies (Table 3.5).



	Additive	Result
1	NMP	boronic acid recovery
2	DMF	boronic acid recovery
3	PPh_3	boronic acid recovery
4	P(*n*-Bu)$_3$	boronic acid recovery
5	$PPh_3(O)$	boronic acid recovery
6	TEA	boronic acid recovery
7	PPTS	boronic acid recovery
8	*p*-TsOH	boronic acid recovery
9	urea	boronic acid recovery
10	$FeCl_3$	boronic acid recovery

Table 3.5. Additive screen with anisidine

The basic additives, like phosphines, amines, and sulfonate (entries 3, 4, 6, and 7) could participate by adding into the boronic acid forming the ate complex and increasing nucleophilicity. Brønsted acidic *p*-TsOH (entry 8) and Lewis acidic $FeCl_3$ (entry 10) might coordinate to the aldehyde and facilitate imine formation, as well as to the imine intermediate, activating it toward nucleophilic addition. Screening both acidic and basic additives, we found that neither chemical class initiated the Petasis reaction, and instead observed complete recovery of boronic acid **3.74**.

Taking a step back, we investigated three different amines in the reaction with ethanol at 60 °C (Figure 3.20). Under these reaction conditions, DAM amine, anisidine, and morpholine were evaluated. Through UPLC-MS monitoring, both DAM amine and anisidine showed no formation of products **3.78** and **3.84**, respectively. The UPLC-MS of the reaction with morpholine contained a small peak bearing the expected $[M+1]^+$ of desired product **3.86**. Though an exciting result, the reaction proceeded in less than 5% conversion, so product isolation proved to be a challenge.

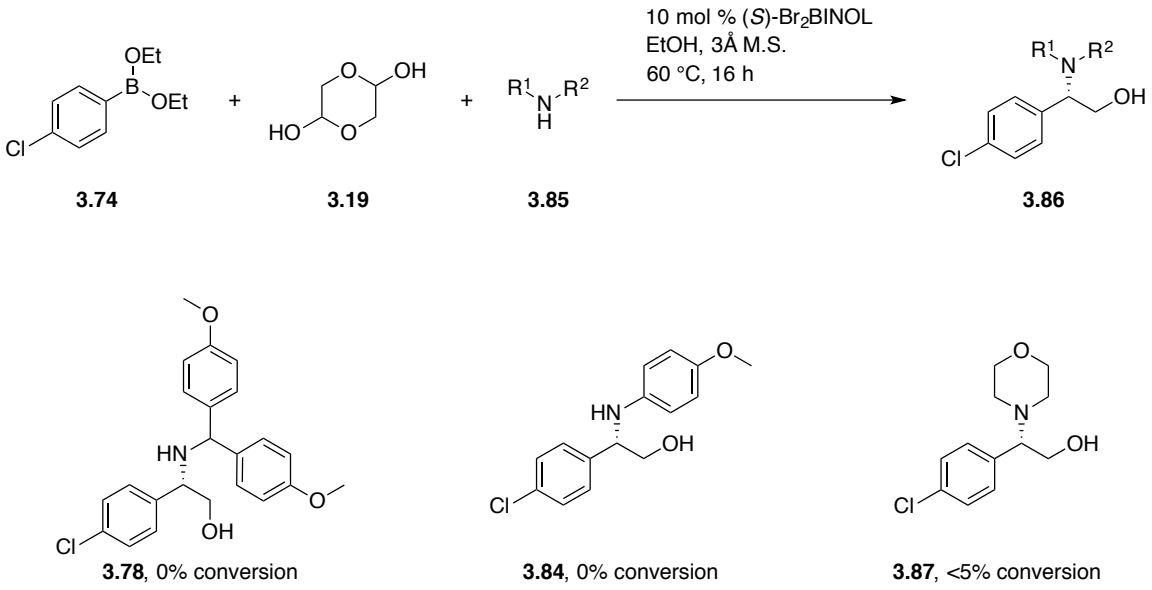


Figure 3.20. Evaluation of different amines in the Petasis reaction with *p*-chlorophenylboronic acid

Regardless, this reaction served as the benchmark for future optimization. Based on McCusker's boronate exchange methodology discussed in Chapter 1[19], we postulated that the addition of triethylborate to the reaction would assist with both boronate/catalyst exchange and imine formation and activation. We began testing this hypothesis by performing an NMR exchange study with *p*-chlorophenylboronic acid, 2 equivalents of triethylborate, and 10 mol % catalyst in deuterated chloroform. Immediately after mixing, an NMR was taken to start monitoring the exchange process. To our delight, we were able to see instantaneous exchange of the ethoxy groups (Figure 3.21). Continued monitoring at 1, 2, and 15 hours showed no significant change in NMR spectra.

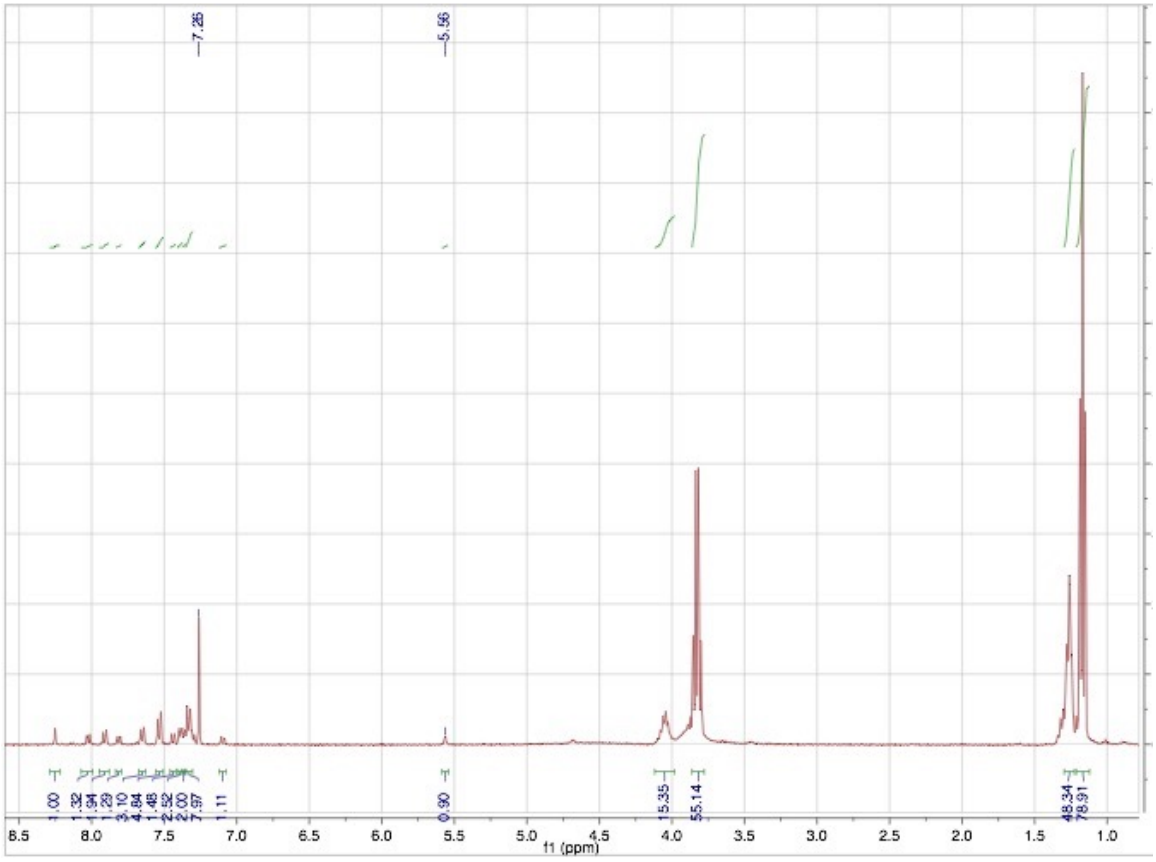
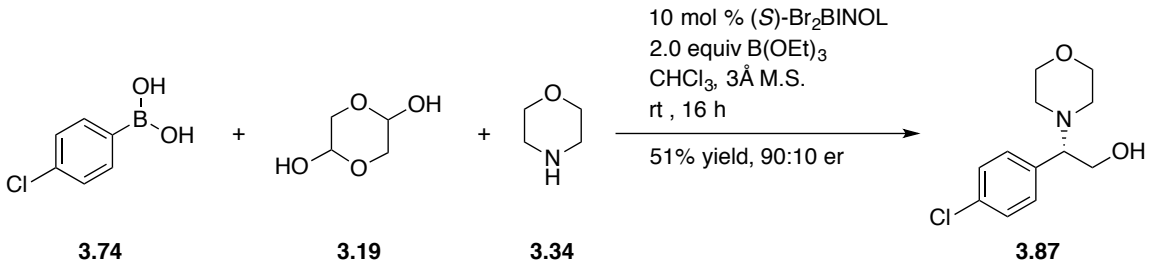


Figure 3.21. NMR exchange study with triethylborate

Following this result, we were optimistic that $B(OEt)_3$ would assist in the formation of the evasive β-amino alcohol product **3.87**. Changing the solvent from ethanol to chloroform, as that was the solvent of the NMR study, the Petasis reaction of *p*-chlorophenylboronic acid with glycolaldehyde dimer **3.19** and morpholine **3.34** was evaluated at room temperature for 16 hours (Figure 3.22). After basic aqueous work-up, amino alcohol **3.87** was isolated in 51% yield with a 90:10 er.



3.74 **3.19** **3.34** **3.87**

Figure 3.22. Triethylborate assisted Petasis reaction of *p*-chlorophenylboronic acid

Proposed Mechanism with Triethylborate

Several reaction factors were changed in order to see the formation of product, so a revised mechanism is needed. Before continuing further with optimization for yield and selectivity, a mechanism accounting for the dual role of triethylborate was proposed (Figure 3.23). The mechanism is similar to that proposed in Chapter 2, with a few minor changes. First, the formation of mixed ester **3.89** occurs from an exchange between boronic acid **3.74** and $B(OEt)_3$. This will single exchange with the substituted BINOL catalyst to give chiral boronate **3.90**. Triethylborate will also act as a Lewis acid and coordinate with the aldehyde monomer, forming the activated **3.91**. This will then undergo nucleophilic addition from morpholine to give the hemiaminal. The β-hydroxyl of **3.92** coordinates to boron's empty *p*-orbital providing ate-complex **3.93**. Following dehydration to the cyclic hemiaminal intermediate, the now nucleophilic boron-carbon bond will add into the electrophilic hemiaminal carbon, generating **3.87** as the desired product.

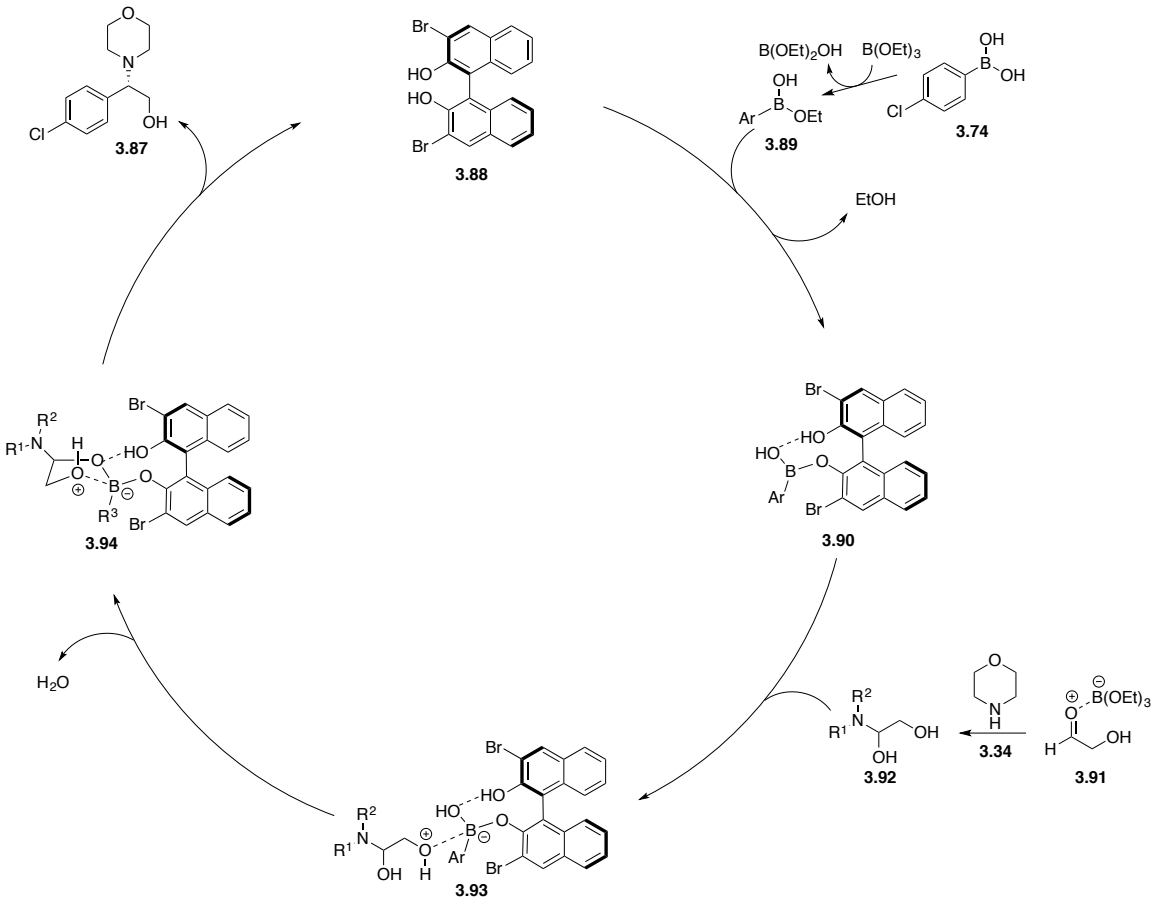


Figure 3.23. Proposed mechanism with triethylborate

Optimization

To begin optimizations, we investigated the role of reaction concentration on yield and selectivity. The original result was obtained using an amine concentration of 0.4 M in chloroform. We hoped by increasing the concentration of the reaction, we could increase the overall rate and subsequently the yield. Increased concentrations of 1.0 M and 2.0 M were evaluated (Figure 3.24). At 1.0 M, the isolated yield of **3.87** decreased from 51% to 38%, and the er remained at 90:10. Further increasing the concentration to

2.0 M led to a larger drop in yield, down to 21% isolated, with a retention of the 90:10 er. It is thought that this drop in yield is due to the rate increase of undesired side reactions with the imine, aldehyde and amine.

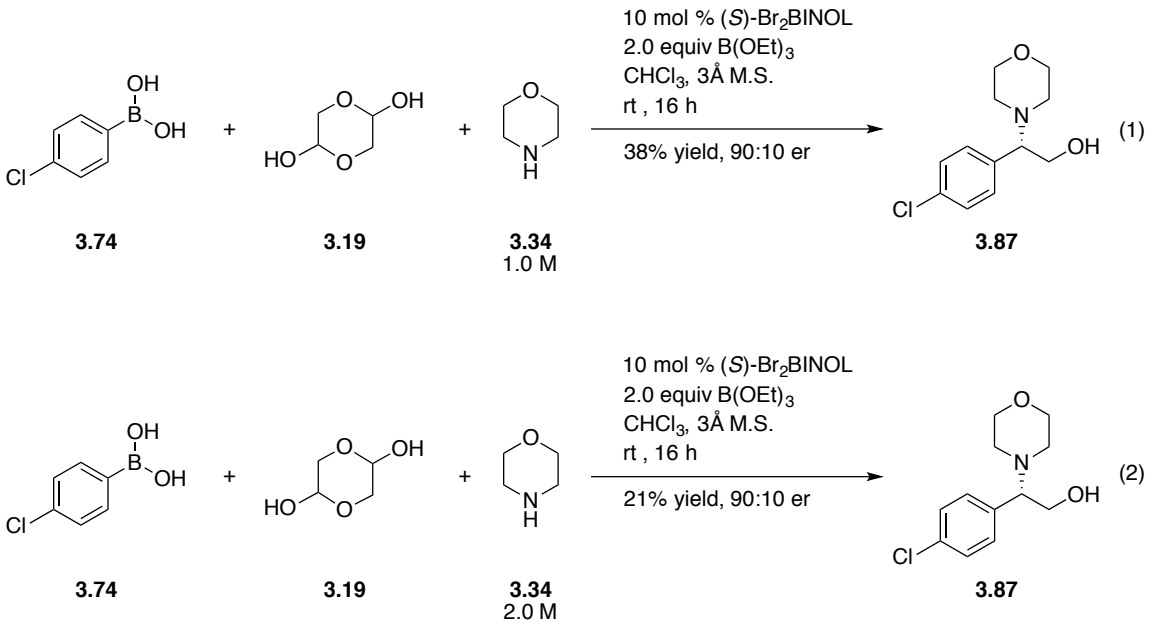


Figure 3.24. Concentration screen for the electron-deficient Petasis reaction

Based on these results, a 0.4 M concentration of the amine was carried forward throughout optimizations. Borate loading was the next condition evaluated. We looked at decreasing the loading down to 1.0 equivalent, 0.5 equivalents, and removing it all together (Figure 3.25). At 1 equivalent of $B(OEt)_3$, there was a drop in yield to 44% and a slight increase in er up to 92:8. Using 0.5 equivalents provided the product in 58% yield, and 92:8 er. Finally, in the absence of borate, the reaction still proceeded, giving the product in 52% yield and 90:10 er.

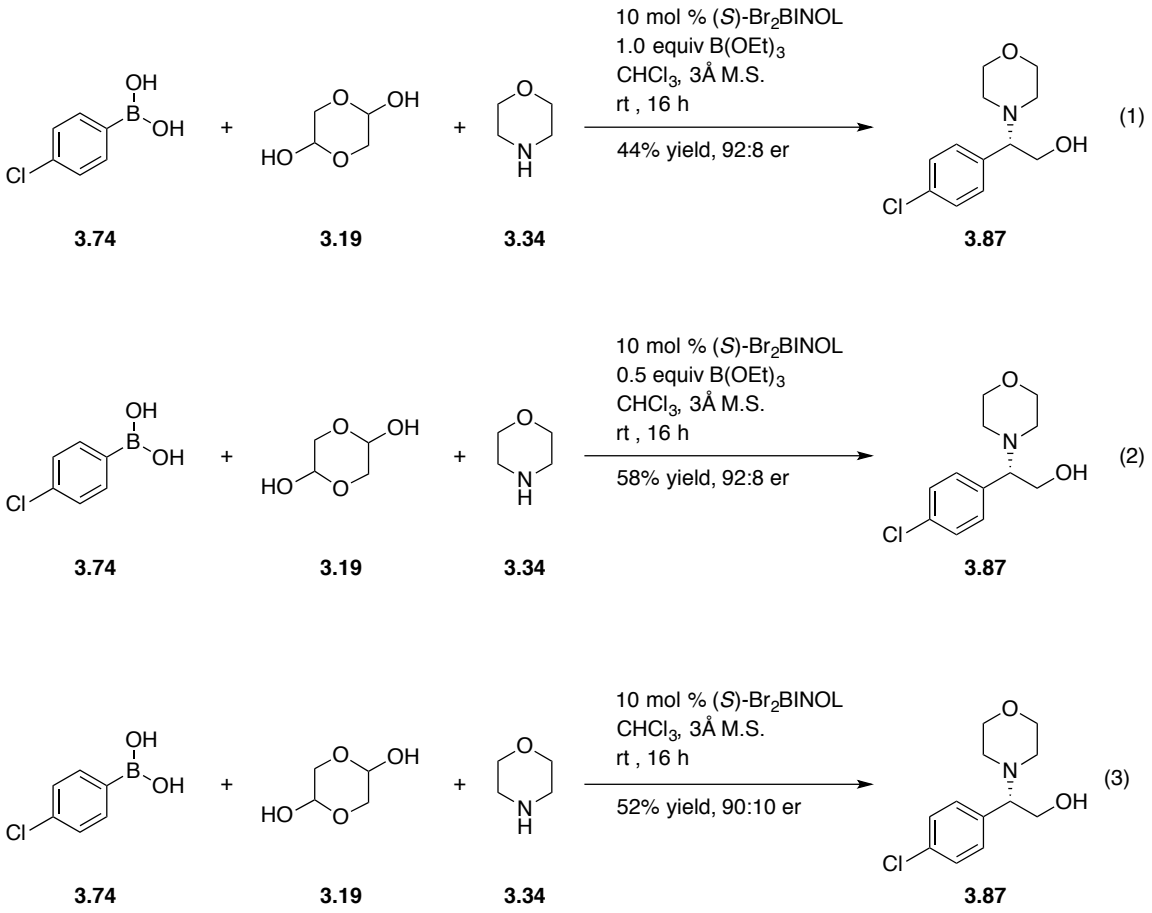


Figure 3.25. Borate loading study

These results indicate that while the reaction can proceed without the borate additive, the best results are obtained with 0.5 equivalents added. From here, we examined the reaction solvent choice. Three other non-coordinating solvents were chosen, DCM, DCE, and $PhCF_3$, along with ethanol as a control (Figure 3.26). DCM, DCE, and trifluorotoluene performed worse in the reaction, providing the product in around 30% isolated yield. Additionally, in DCM the er dropped to 88:12, and in DCE it was 90:10. Trifluorotoluene, while producing a lower yielding reaction, exhibited an

enhanced selectivity of 95:5 er. As expected, the coordinating solvent, ethanol, only gave the product in 9% isolated yield.

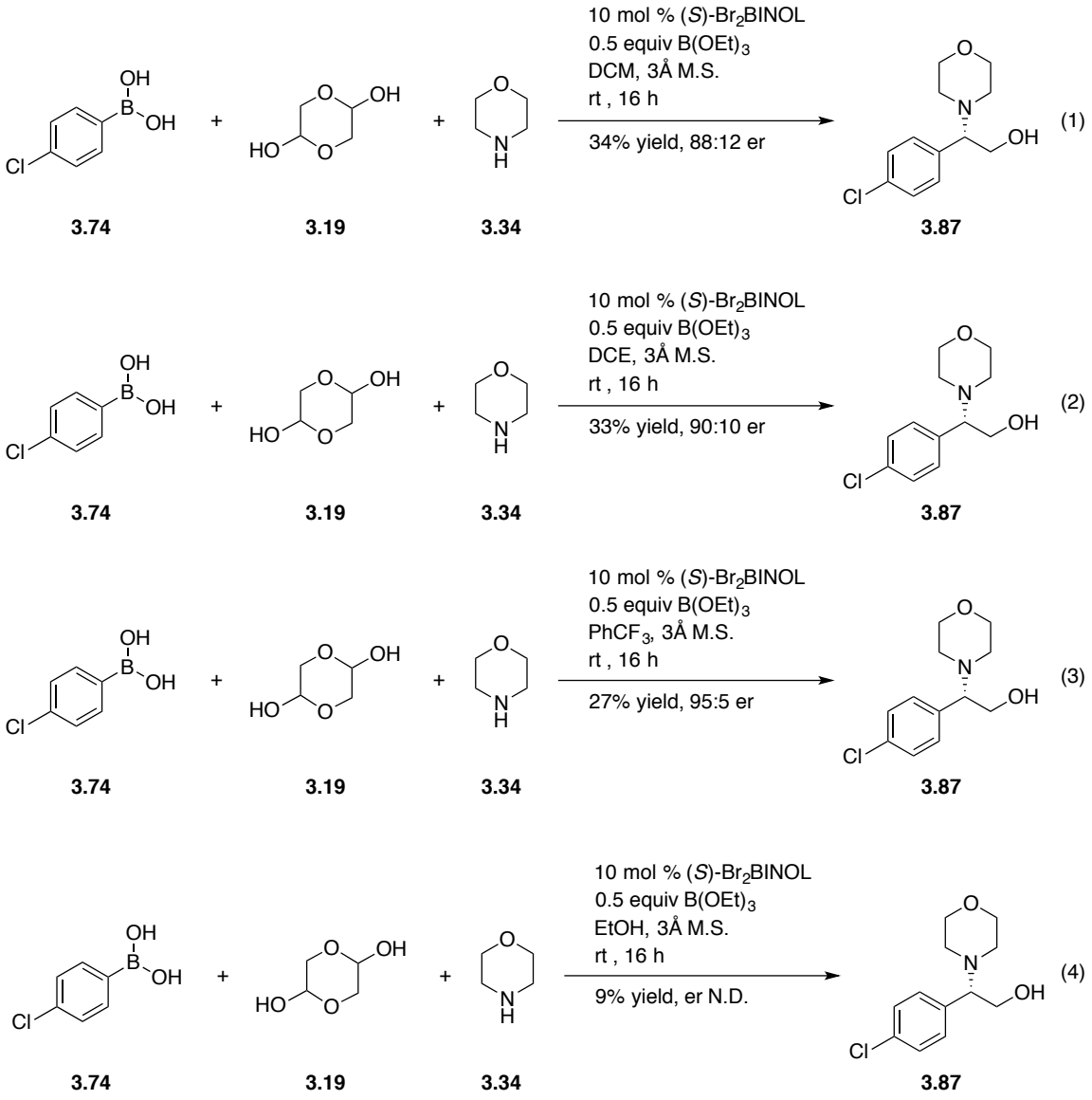


Figure 3.26. Evaluation of solvents in the electron-deficient Petasis reaction

Substrate Scope

Satisfied with the results of 58% yield and 92:8 er for *p*-chlorophenylboronic acid, we turned to investigating other halogenated aromatic boronic acids. Compound **3.95** was isolated in 58% yield and 90:10 er from reaction with *p*-bromophenylboronic acid **3.18** (Figure 3.27). Fluorinated boronic acid performed exceptionally better, providing product **3.97** in 75% yield and 92:8 er. Likewise, unsubstituted phenylboronic acid gave **3.99** in 75% yield and 92:8 er.

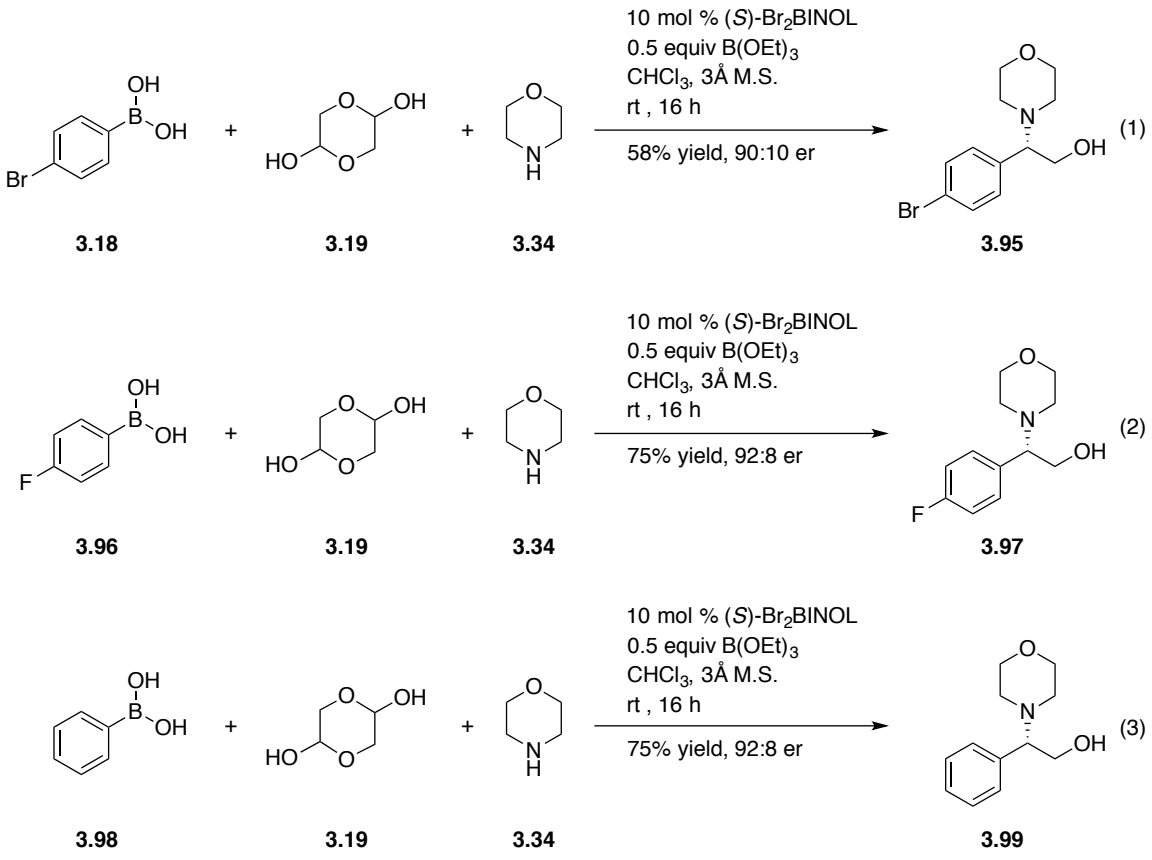


Figure 3.27. Halogenated boronic acids in the Petasis reaction

With all selectivities below 95:5 er, there remained room for improvement. To enhance the chiral environment, the 3,3'-bromo substituents on the BINOL were replaced with phenyl groups through a Suzuki coupling, and this new sterically and electronically different catalyst was tested in the previously optimized conditions. Much to our delight, the results were improved due to this substitution (Figure 3.28). Chlorinated boronic acid **3.74** provided the corresponding amino alcohol in 57% yield and 93:7 er. Although slightly increased, these results are comparable to those with (*S*)-Br_2BINOL. The *p*-bromophenylboronic acid gave **3.95** in both an increased yield of 67% and enantioselectivity of 95:5 er. Fluorophenyl β-amino alcohol **3.97** was obtained in 85% yield and 95:5 er, and unsubstituted **3.99** was formed in 70% yield and 94:6 er.

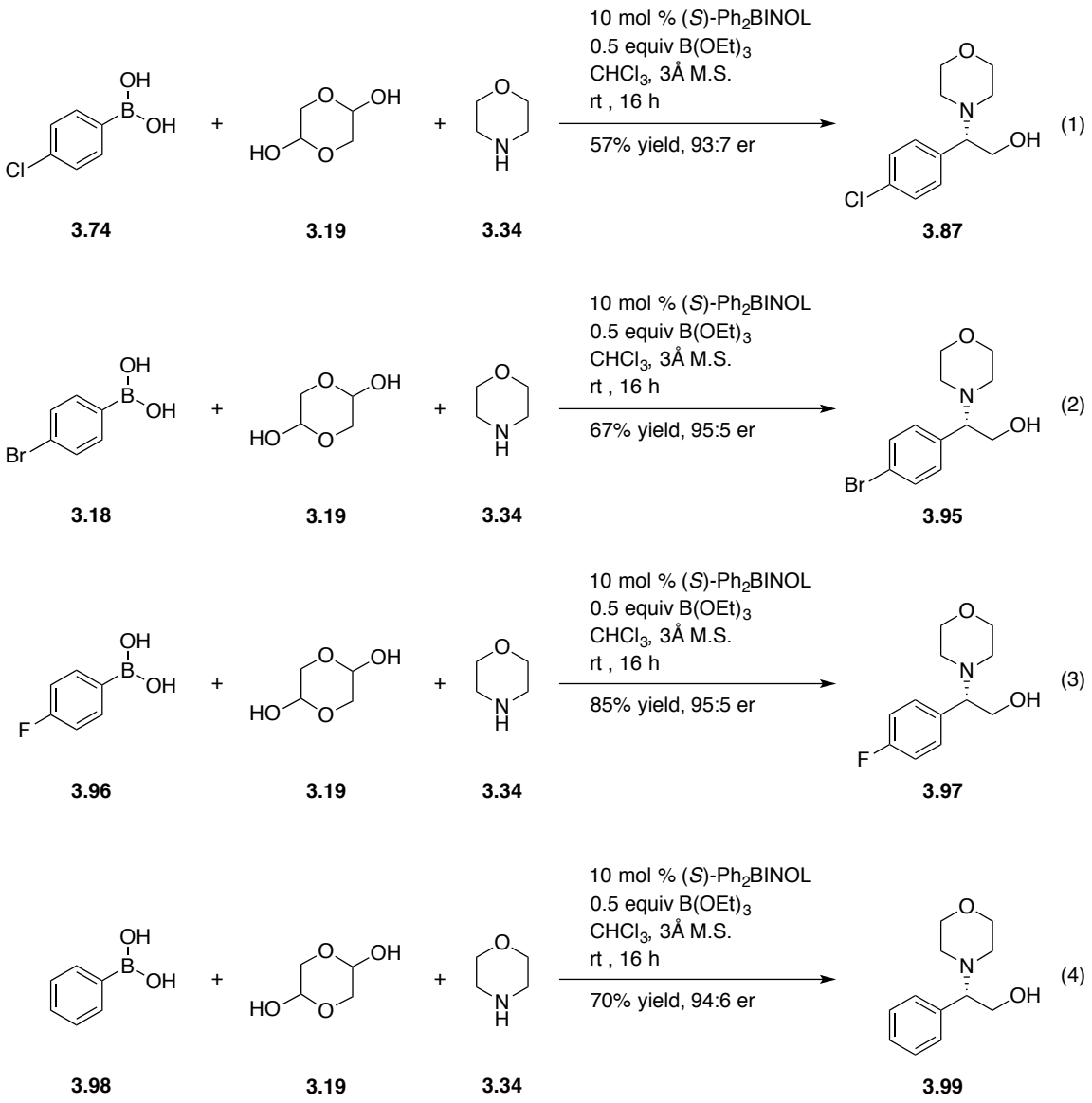


Figure 3.28. Optimized substrate scope for the electron-deficient Petasis reactions

Conclusion

In conclusion, we have developed an enantioselective Petasis reaction of glycolaldehyde dimer with electron-deficient aromatic boronates. Through incremental optimization, we were able to find conditions which promoted the formation of aryl β-amino alcohols with halogenated boronic acids. Using a cyclic secondary amine, chloroform as a solvent, and triethylborate as an additive, products were obtained in yields up to 85% and enantioselectivities up to 95:5 er. Each of the reaction components that were changed played a significant role in affecting the transformation.

By using a cyclic secondary amine, two reactive qualities were adjusted. First, the use of a cyclic amine provides reduced rotation around the nitrogen, and therefore a more directed lone pair. This affixing of the lone pair in space makes it more nucleophilic and allows for easier formation of the imine. Secondly, because of its nature as a secondary amine, the intermediate that is formed through condensation of the amine onto the aldehyde is a charged iminium as opposed to a neutral imine. The positive charge on the iminium intermediate renders it more electrophilic, and therefore more reactive towards nucleophilic addition by the boronate.

The use of chloroform as a solvent eliminates the possibility of solvent/boronate coordination like is expected with ethanol. This coordination could coordinatively saturate the boron preventing it from further exchanging with catalyst and moving forward in the reaction. Furthermore, due to the inductively electron withdrawing characteristic of halogens, the boron-oxygen bonds and boron-carbon bonds would be stronger, and less likely to be given up. While the switch to a non-coordinating solvent

like chloroform did increase reactivity, this enhancement cannot be solely contributed to its non-coordinating properties as other similar solvents ($PhCF_3$, DCM, and DCE) did not produce the same effect. It is postulated that the trace amounts of HCl found in stock bottles of chloroform are also aiding in the formation of product.

Finally, the addition of triethylborate in the reaction has a two-fold effect on the overall reactivity. First, it can act as a Lewis acid, accepting electrons from the aldehyde monomer and activating it towards nucleophilic addition by the amine to form the hemiaminal. Second, it also exchanges with the hydroxyls on the boronic acid, making the ester or mixed ester, which then goes on to more rapidly exchange with the BINOL catalyst. This ligand exchange was observed by ^1H NMR.

The combination of these three chemical entities in the reaction proved to effectively promote the Petasis reaction of halogenated and unsubstituted aromatic boronic acids. Through this optimization, we have expanded the scope of our previously developed Petasis reaction of glycolaldehyde to include a set of electronically diverse boronate nucleophiles in the synthesis of β-amino alcohols.

Experimental Information

General Information

All ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Unity Plus 500 MHz spectrophotometer at ambient temperature in $CDCl_3$. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Low resolution mass spectrometry data was obtained on an Agilent LC/MSD VL system by electrospray (ESI) flow injection analysis in the positive mode. Mobile phases were water and acetonitrile with 0.1% formic acid. The MS settings were: voltage = 3000V, fragmentor = 70 and chamber temperature = 350 °C. UPLC-MS analysis was performed on a C18 column (1.7mm, 2.1 X 50 mm) with CH_3CN:H_2O gradient as eluent with UV, ELSD and electrospray ionization (ESI) positive ion detection. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]_D$ (concentration in grams/100mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC System with a diode array detector. Chiral columns include Chiralcel® OD (Chiral Technologies Inc., 25 cm x 4.6 mm I.D.), Chiralpak® AD-H (Chiral Technologies Inc., 25 cm x 4.6 mm I.D.), Chiralpak® IA (Chiral Technologies Inc., 24 cm x 4.6 cm I.D.) and (*R,R*)-Whelk-O (Regis® Technologies Inc., 25 cm x 4.6 mm I.D.).

General Procedure for the Preparation of Diethyl Boronates

Boronate esters were prepared according to the literature[53] with slight modifications. To a 250 mL RBF was added a stir bar, 15 g 4Å M.S., and 15 g $MgSO_4$. The flask was then sealed with a rubber septa and flame dried under vacuum. The flask was allowed to cool to room temperature under argon and to it was added 1.5 g *p*-chlorophenylboronic acid, 40 mL of ethanol, and 80 mL of chloroform. The reaction was heated to reflux for 48 hours under Ar. After 48 hours, the reaction was then cooled to room temperature and vacuum filtered under a steady stream of nitrogen gas through a sintered glass funnel into a new 250 mL RBF, that were both dried in the oven overnight. The solution was then concentrated on the rotovap to ~10 mL. The rotovap was purged with an argon balloon and the resultant liquid transferred *via* syringe to a tared, flame dried crimp vial containing a micro stir bar. The solution was further concentrated under high vac with stirring to a constant mass (~2 hours). The resultant liquid boronate was measured and anhydrous $PhCH_3$ was added to make a 2.0 or 4.0 M solution. The vial was stored under Argon, in the refrigerator.

General Procedure for the Petasis reaction of Electron-Deficient Boronic Acids

An oven dried reaction tube was charged with a stir bar and to it was added *p*-chlorophenylboronic acid (0.20 g, 1.3 mmol), glycolaldehyde dimer (0.060 g, 0.50 mmol), (*S*)-Ph_2BINOL (0.057 g, 0.13 mmol), and 3Å M.S. (500 mg). The reaction was equipped with a rubber septum, kept under Ar, and to it was added morpholine (0.087 mL, 1.0 mmol), triethylborate (0.085 mL, 0.50 mmol), and chloroform (2.5 mL). The

reaction was stirred at room temperature for 16 h. The reaction mixture was then dissolved in a small amount of DCM and transferred to a 250 mL separatory funnel. To it was added 75 mL 2M NaOH and 40 mL DCM. The organic layer was extracted and the aqueous layer washed twice more with DCM. The organic layers were pooled, dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product as a mixture with (*S*)-Ph_2BINOL. The residue was then loaded into silica and purified over a short silica plug, elution with 10 -> 30% EtOAc in hexanes to yield the product as a viscous oil (0.138 g, 57%). **er =** 93:7. **$[\alpha]_D$** = +21.2° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.90 (dd, *J* = 11.0, 8.2 Hz, 1H), 3.73 – 3.67 (overlap, 5H), 3.55 (dd, *J* = 8.2, 5.1 Hz, 1H), 2.65 (brs, OH), 2.52 (m, 2H), 2.39 (m, 2H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 134.73, 133.97, 130.15, 128.68, 70.00, 67.20, 60.82, 50.06. **UPLC-MS** (ESI^+) *m/z* calc'd for $[C_{12}H_{16}ClNO_2+H]^+$ 242.09, found 242.1.

(S)-2-(4-bromophenyl)-2-morpholinoethan-1-ol ***(3.95)***

This compound was prepared according to the general procedure using 4-bromophenylboronic acid (0.26 g, 1.3 mmol) to afford to product as a viscous oil (0.192 g, 67%). **er =** 95:5. **$[\alpha]_D$** = +19.0° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 3.90 (dd, *J* = 11.1, 8.2 Hz, 1H), 3.74 – 3.68 (overlap, 5H), 3.54 (dd, *J* = 8.2, 5.1 Hz, 1H), 2.52 (m, 2H), 2.38 (m, 2H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 135.29, 131.65, 130.50, 122.11, 70.07, 67.22, 60.78, 50.08. **UPLC-MS** (ESI^+) *m/z* calc'd for $[C_{12}H_{16}BrNO_2+H]^+$ 286.04, found 286.0.

(S)-2-(4-fluorophenyl)-2-morpholinoethan-1-ol ***(3.97)***

This compound was prepared according to the general procedure using 4-fluorophenylboronic acid (0.18 g, 1.3 mmol) to afford to product as a viscous oil (0.191 g, 85%). **er =** 95:5. $[\alpha]_D$ = +22.3° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.19 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.05 (dd, *J* = 8.6, 8.6 Hz, 2H), 3.92 (dd, *J* = 10.9, 8.5 Hz, 1H), 3.75 – 3.66 (overlap, 5H), 3.58 (dd, *J* = 8.5, 5.1 Hz, 1H), 2.68 (s, OH), 2.53 (m, 2H), 2.39 (m, 2H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 163.56, 161.59, 131.78, 131.75, 130.45, 130.39, 115.50, 115.33, 69.87, 67.21, 60.83, 49.96. **UPLC-MS** (ESI^+) *m/z* calc'd for $[C_{12}H_{16}FNO_2+H]^+$ 226.12, found 226.1

(S)-2-phenyl-2-morpholinoethan-1-ol ***(3.99)***

This compound was prepared according to the general procedure using phenylboronic acid (0.16 g, 1.3 mmol) to afford to product as a viscous oil (0.145 g, 67%). **er =** 94:6. $[\alpha]_D$ = +21.9° (c = 1.0, $CHCl_3$). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.37 – 7.31 (overlap, 3H), 7.21 (dd, *J* = 8.0, 1.5 Hz, 2H), 3.97 (dd, *J* = 11.0, 8.7 Hz, 1H), 3.74 – 3.69 (overlap, 5H), 3.61 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.08 (m, OH), 2.57 (m, 2H), 2.41 (m, 2H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 135.75, 128.94, 128.49, 128.21, 70.64, 67.22, 60.69, 49.97. **UPLC-MS** (ESI^+) *m/z* calc'd for $[C_{12}H_{17}NO_2+H]^+$ 208.13, found 208.1.

LIST OF JOURNAL ABBREVIATIONS

Acc. Chem. Res. ..... Accounts of Chemical Research

Adv. Synth. Catal. ..... Advanced Synthesis and Catalysis

Anal. Chim. Acta ..... Analytica Chimica Acta

Angew. Chem. Int. Ed. ..... Angewandte Chemie International Edition

Angew. Chem. Int. Ed. Eng. ..... Angewandte Chemie International Edition in English

Antimicrob. Agents Chemother. ..... Antimicrobial Agents and Chemotherapy

B. Rev. ..... Book Reviews

Berichte der Dtsch. Chem. Gesellschaft .. Berichte der deutschen chemischen Gesellschaft

Bioorganic Med. Chem. ..... Bioorganic Medicinal Chemistry

Bull. Chem. Soc. Jpn. ..... Bulletin of the Chemical Society of Japan

Carbohydr. Res. ..... Carbohydrate Research

Chem. Abstr. ..... Chemical Abstracts

Chem. Asian J. ..... Chemistry, An Asian Journal

Chem. Commun. ..... Chemical Communications

Chem. – A Eur. J. ..... Chemistry: a European Journal

Chem. Rev. ..... Chemical Reviews

Chem. Soc. Rev. ..... Chemical Society Reviews

Chinese J. Chem. ..... Chinese Journal of Chemistry

Eur. J. Med. Chem. ..... European Journal of Medicinal Chemistry

Eur. J. Org. Chem. ..... European Journal of Organic Chemistry

Inorg. Chem. ..... Inorganic Chemistry

J. Am. Chem. Soc. ..... Journal of the American Chemical Society

J. Am. Soc. Mass Spectrom. .....Journal of the American Chemical Society for .....Mass Spectrometry

J. Chem. Phys.....Journal of Chemical Physics

J. Chem. Res. ..... Journal of Chemical Research

J. Med. Chem. .....Journal of Medicinal Chemistry

J. Org. Chem. .....Journal of Organic Chemistry

J. Phys. Org. Chem. ..... Journal of Physical Organic Chemistry

Org. Lett. .....Organic Letters

Proc. Natl. Acad. Sci. ..... Proceedings of the National Academy of Sciences

Prog. Med. Chem. .....Progress in Medicinal Chemistry

Tetrahedron Lett.....Tetrahedron Letters

Thromb. Haemost. ..... Journal of Thrombosis and Haemostasis

BIBLIOGRAPHY

(1) Gregory, R. J. H. *Chem. Rev.* **1999**, *99* (12), 3649.

(2) North, M. *Synlett* **1993**, 807.

(3) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146.

(4) Kiliani, H. *Berichte der Dtsch. Chem. Gesellschaft [Abteilung] B Abhandlungen* **1931**, *64B*, 2018.

(5) Varma, R.; French, D. *Carbohydr. Res.* **1972**, *25* (1), 71.

(6) Humphrey, G. R.; Pye, P. J.; Zhong, Y. L.; Angelaud, R.; Askin, D.; Belyk, K. M.; Maligres, P. E.; Mancheno, D. E.; Miller, R. A.; Reamer, R. A.; Weissman, S. A. *Org. Process Res. Dev.* **2011**, *15* (1), 73.

(7) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40* (46), 8147.

(8) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122* (30), 7412.

(9) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129* (51), 15872.

(10) Kraus, G. A.; Shimagaki, M. *Tetrahedron Lett.* **1981**, *22* (13), 1171.

(11) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48* (10), 1690.

(12) Soldermann, C. P.; Vallinayagam, R.; Tzouros, M.; Neier, R. *J. Org. Chem.* **2008**, *73*, 764.

(13) Chaperon, A. R.; Engeloch, T. M.; Neier, R. *Angew. Chemie Int. Ed.* **1998**, *37* (3), 358.

(14) Alam, R.; Raducan, M.; Eriksson, L.; Szabó, K. J. *Org. Lett.* **2013**, *15* (10), 2546.

(15) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew Chem Int Ed Engl* **2009**, *48* (46), 8679.

(16) Barnett, D. S.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4020.

(17) Lou, S.; Moquist, P. N.; Schaus, S. E. *J Am Chem Soc* **2006**, *128* (39), 12660.

(18) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.

(19) McCusker, P. A.; Pennartz, P. L.; Pilger, Richard C., J. *B. Rev.* **1962**, 4362.

(20) Wood, A.; Armour, D. *Prog. Med. Chem.* **2005**, *43*, 239.

(21) Dorr, P.; Westby, M.; Dobbs, S.; Griffin, P.; Irvine, B.; Macartney, M.; Mori, J.; Rickett, G.; Smith-Burchnell, C.; Napier, C.; Webster, R.; Armour, D.; Price, D.; Stammen, B.; Wood, A.; Perros, M. *Antimicrob. Agents Chemother.* **2005**, *49* (11), 4721.

(22) Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* **1982**, *21* (1), 36.

(23) Hart, H.; Karabatsos, G. J. *Advances in Alicyclic Chemistry, Volume 3*; Elsevier Science, 2013.

(24) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006.

(25) Schrader, T. *Angew. Chemie Int. Ed. English* **1995**, *34* (8), 917.

(26) Schrader, T. *Chem. - A Eur. J.* **1997**, *3* (8), 1273.

(27) Louzao, I.; Garcia, R.; Seco, J. M.; Quinoa, E.; Riguera, R. *Org. Lett.* **2009**, *11* (1), 53.

(28) Louzao, I.; Seco, J. M.; Quinoa, E.; Riguera, R. *Chem Commun* **2006**, No. 13, 1422.

(29) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55* (6), 1868.

(30) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6* (16), 2701.

(31) Kindon, N.; Mete, A.; Teobald, B. Novel N-Pyrazinil-phenylsulfonamide derivatives as chemokine receptor modulators for use in the treatment of asthma. WO 2007/035154 A1, 2007.

(32) Keana, J.; Ordentlich, P.; Goodenow, R. Novel compounds and methods of using them. WO 2009/015237 A1, 2009.

(33) Dzierba, Carolyn, D.; Hartz, R. A.; Bi, Y.; Ahuja, V. T.; Bronson, J. J.; Carson, K.; Cianchetta, G.; Green, M.; Kimball, D.; Kimura, S. R.; Kwon, S.; Macor, J. E.; Zhang, Y.; Zipp, G. Modulators of G Protein-coupled receptor 88. WO 2011/044225 A1, 2011.

(34) Bello, C.; Cea, M.; Bello, G. D.; Garuti, A.; Rocco, I.; Cirmena, G.; Moran, E.; Nahimana, A.; Duchosal, M. A.; Fruscione, F.; Pronzato, P.; Grossi, F.; Patrone, F.; Ballestrero, A.; Dupuis, M.; Sordat, B.; Nencioni, A.; Vogel, P. *Bioorganic Med. Chem.* **2010**, *18* (9), 3320.

(35) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.

(36) Eskildsen, J.; Redrobe, J. P.; Sams, A. G.; Dekermendjian, K.; Laursen, M.; Boll, J. B.; Papke, R. L.; Bundgaard, C.; Frederiksen, K.; Bastlund, J. F. *Bioorganic Med. Chem. Lett.* **2014**, *24* (1), 288.

(37) Bandini, M.; Cozzi, G.; Gazzano, M.; Umani-ronchi, A. *European J. Org. Chem.* **2001**, 1937.

(38) Reddy, K. L.; Sharpless, K. B. *J Am Chem Soc* **1998**, *120*, 1207.

(39) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J. H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122* (30), 7416.

(40) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J. H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862.

(41) Dzierba, C. D.; Bi, Y.; Dasgupta, B.; Hartz, R. A.; Ahuja, V.; Cianchetta, G.; Kumi, G.; Dong, L.; Aleem, S.; Fink, C.; Garcia, Y.; Green, M.; Han, J.; Kwon, S.; Qiao, Y.; Wang, J.; Zhang, Y.; Liu, Y.; Zipp, G.; Liang, Z.; Burford, N.; Ferrante, M.; Bertekap, R.; Lewis, M.; Cacace, A.; Grace, J.; Wilson, A.; Nouraldeen, A.; Westphal, R.; Kimball, D.; Carson, K.; Bronson, J. J.; Macor, J. E. *Bioorganic Med. Chem. Lett.* **2015**, *25* (7), 1448.

(42) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34* (4), 583.

(43) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110* (10), 6169.

(44) Monk, J. P.; Brogden, R. N. *Drugs* **1991**, *42* (4), 659.

(45) Sağırli, A.; Dürüst, Y.; Kariuki, B.; Knight, D. W. *Tetrahedron* **2013**, *69* (1), 69.

(46) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112* (6), 3083.

(47) Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M. *Org. Lett.* **2013**, *15* (1), 148.

(48) Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14* (4), 976.

(49) Han, W.-Y.; Zuo, J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2013**, *69* (2), 537.

(50) Inokuma, T.; Suzuki, Y.; Sakaeda, T.; Takemoto, Y. *Chem Asian J* **2011**, *6* (11), 2902.

(51) Shi, X.; Kiesman, W. F.; Levina, A.; Xin, Z. *J. Org. Chem.* **2013**, *78* (18), 9415.

(52) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129* (21), 6686.

(53) Lou, S.; Schaus, S. E. *J Am Chem Soc* **2008**, *130* (22), 6922.

(54) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115* (9), 3814.

(55) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120* (45), 11798.

(56) Muncipinto, G.; Moquist, P. N.; Schreiber, S. L.; Schaus, S. E. *Angew Chem Int Ed Engl* **2011**.

(57) Keller, B. O.; Sui, J.; Young, A. B.; Whittal, R. M. *Anal. Chim. Acta* **2008**, *627* (1), 71.

(58) Tong, H.; Bell, D.; Tabei, K.; Siegel, M. M. *J. Am. Soc. Mass Spectrom.* **1999**, *10* (11), 1174.

(59) Lan, H.; Ruan, Y.; Huang, P. *Chem Comm* **2010**, *46*, 5319.

(60) Levin, D. In *ACS Symposium Series*; 2014; pp 3–71.

(61) Wrightson, I.; Cooper, S. J.; Crookes, M.; King, N.; Lewis, P.; Larner, J.; Lohmann, D. H.; Maxwell, C.; Sanderson, D. M.; Jackson, P.; Whitehead, S.; Grundy, C.; Watts, C.; Lipworth, S.; Dempsey, C. **2013**, *3*.

(62) Savi, P.; Pereillo, J. M.; Uzabiaga, M. F.; Combalbert, J.; Picard, C.; Maffrand, J. P.; Pascal, M.; Herbert, J. M. *Thromb Haemost* **2000**, *84* (5), 891.

(63) Alla, V. R.; Vyakaranam, K. R.; Sirigiri, A. K.; Bodapati, S. R.; Billa, R. R.; Gudibandi, S. R.; Alla, R. Process for Preparation of Clopidogrel Bisulphate Form-1. US 2007/0191609 A1, 2007.

(64) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synthesis (Stuttg).* **2008**, No. 24, 4007.

(65) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53* (48), 16463.

(66) McLean, N. J.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45* (5), 993.

(67) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46* (12), 2025.

(68) Zhao, L.; Liao, X.; Li, C. J. *Synlett* **2009**, No. 18, 2953.

(69) Naskar, D.; Neogi, S.; Roy, A.; Mandal, A. B. *Tetrahedron Lett.* **2008**, *49* (48), 6762.

(70) Liu, Y.; Wang, L.; Sui, Y.; Yu, J. *Chinese J. Chem.* **2010**, *28* (10), 2039.

(71) Thompson, K. A.; Hall, D. G. *Chem. Commun.* **2000**, No. 23, 2379.

(72) Follmann, M.; Graul, F.; Schäfer, T.; Kopec, S.; Hamley, P. *Synlett* **2005**, No. 6, 1009.

(73) Gaussian http://www.gaussian.com/g_tech/g_ur/k_dft.htm (accessed Oct 21, 2015).

CURRICULUM VITAE

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EDUCATION

- *Ph.D. Boston University*, Organic Chemistry, Boston, MA, June 2016
- *M.A. Boston University*, Organic Chemistry, Boston, MA, May 2012
- *B.S. St. Michael's College*, Chemistry, *magna cum laude,* Colchester, VT, May 2010

SCIENTIFIC EXPERIENCE

Research assistant, *Boston University*, Boston, MA October 2010 – current
Professor Scott E. Schaus, Ph.D., research advisor

- Expanded methodology for asymmetric allylborations of acyl cyanides
  - Built substrate table of varying acyl cyanides
- Optimized the first asymmetric synthesis of β-amino alcohols *via* the Petasis Reaction
  - Synthesized small library by varying the amino and boronic acid components
  - Performed MS-guided mechanistic studies
  - Conducted scale-up studies to determine retention of enantioselectivity
  - Optimized reaction conditions to include weakly reactive nucleophiles into the substrate scope
- Performed preliminary studies for an asymmetric allene synthesis *via* the Petasis Reaction
  - Established reactivity with alkynyl boronates
  - Performed condition and catalyst optimization screens for enantioselectivity

Research assistant, *St. Michael's College*, Colchester, VT Summer 2009, Summer 2008
Professor Shane M. Lamos, Ph.D., research advisor

- Progress towards the development of an isotopically labeled Si-containing metabolite labeling reagent
- Set up new lab research space

Laboratory Prep assistant, *St. Michael's College*, Colchester, VT September 2006 – May 2010
Jennifer Paone-Vogt, M.S., work study advisor

- Prepared standard solutions and unknown samples for teaching labs

TEACHING EXPERIENCE

Teaching Fellow, *Boston University*, Boston, MA September 2010 – current

- Organic Chemistry discussion and lab sections
- Biochemistry pre-lab discussion and labs

PUBLICATIONS AND PRESENTATIONS

- **Summo, K. E.;** Demerzhan, R.; Moquist, P. N.; Schaus, S. E. "Enantioselective Petasis Reaction of Glycolaldehyde Dimer Catalyzed by Chiral Biphenols." *Manuscript in Preparation*.
- **Summo, K. E.;** Barnett, D. S.; Schaus, S.E. "Asymmetric Allylboration of Acyl Cyanides Cayalyzed by Chiral Biphenols." *Manuscript in Preparation*.
- **Summo, K. E.;** Demerzhan, R.; Moquist, P. N.; Schaus, S. E. "Enantioselective Petasis Reaction of Glycolaldehyde Dimer Catalyzed by Chiral Biphenols." *Oral Presentation*, 248th American Chemical Society National Meeting, San Francisco, CA, August 12, 2014.
- Schaus, S. E.; **Summo, K. E.;** Keil, H. C.; McHale, P. J. "Technology Will Challenge the Existing Paradigm for Teaching Organic Chemistry: 3D Printing, Tablets, and Gamification in Boston University's Spring 2014 CH212." *Oral Presentation*, 248th American Chemical Society National Meeting, San Francisco, CA, August 12, 2014.
    - Interactive demonstration of ChemDraw for iPad and Flick-2-Share feature

SCIENTIFIC INSTRUMENTATION & SOFTWARE SKILLS

- Mass Spectrometry (LC/MS and FIA/MS)
- Ultra Pure Liquid Chromatography/Mass Spectrometry
- Chiral High Purity Liquid Chromatography
- Nuclear Magnetic Resonance Spectroscopy (^{1}H, ^{13}C, ^{11}B, ^{19}F, APT, and 2D experiments)
- ISCO Combiflash Chromatography
- Microwave Synthesis
- Fourier Transform Infrared Spectroscopy
- Ultraviolet/Visible Spectroscopy
- ChemDraw (Desktop and iPad versions, in both research and teaching)
- Scifinder
- Electronic Notebooks (Elements, ArtusLabs, and Scilligence)

LEADERSHIP

- President, Boston University Women in Chemistry, June 2013 – May 2014
- Outreach Coordinator, Boston University Women in Chemistry, June 2012 – May 2013
- Organizer, BU Chemistry Department Annual Chemistry Day, May 2013/2014
- Mentor, Three undergraduate and one high school research students

HONORS/ACHIEVEMENTS

- Recipient, Outstanding Teaching Fellow Award, May 2015
- Recipient, Vertex Conference Support Grant, August 2014
- Recipient, Paul Winslow Chemistry Endowment, Summer Research 2009
- Member, Sigma Xi – Scientific Research Society, Inducted April 2010
- Member, Pi Mu Epsilon – Mathematics Honor Society, Inducted April 2010